Pavlovian Society
Annual Meeting, 2016
Hyatt Regency Jersey City

Sept 29–Oct 1, 2016
Jersey City, NJ

Overview

Thur	6:00–10:00 PM	Opening Reception Riverside & Riverside Terrace Hors d'Oeuvres & Cash Bar Music at 8:00 by ***So We Are*** (Joe LeDoux & Colin Dempsey)
Fri	7:30–8:25	Breakfast
	8:25–Noon	Morning Sessions
	12:05–1:30	Lunch (Exec Committee Meeting)
	1:30–5:15	Afternoon Sessions
	5:30–7:30	Posters & Cash Bar
Sat	7:30–8:25	Breakfast
	8:25–12:05	Morning Sessions
	12:05–1:40	Lunch (WIL Luncheon)
	1:40–5:10	Afternoon Sessions
	5:30–7:30	Posters & Cash Bar
	7:30–9:00	Banquet

Program

Friday (Sept 30)

7:30–8:25 Breakfast
Hudson Hallway

Sessions in Hudson IV, V, VI

8:25–8:30 Welcome: **Andrew Delamater** *Brooklyn-CUNY*

8:30–9:30 ***Keynote Address:***
John Pearce *Cardiff*: A new look at an old theory

9:30–9:55 **Peter Holland** *Johns Hopkins*: Effects of amygdala lesions on overexpectation phenomena in food cup approach and autoshaping procedures

9:55–10:20 **Rob Honey** *Cardiff*: Learning about stimuli that are present and those that are not: Dissociating direct and mediated learning

10:20–10:40 Coffee Break

10:40–11:05 **Jonathon Crystal** *Indiana U*: Animal models of episodic memory

11:05–12:05 ***Symposium: New Invertebrate Contributions to the Study of Learning and Memory***

– **David Glanzman, Pearce K, Cai D, Chen S** *UCLA*: Role of DNA Methylation in the Maintenance of Long-Term Memory in Aplysia

– **Scaplen KM, Bounds HA, Ekins TG, Huynh S, Savory N, Kaun KR** *Brown*: Mapping neural circuits for alcohol reward memories in Drosophila

– **Catharine Rankin** *U British Columbia*: Redefining habituation as a change in response strategy

12:05–1:30 Lunch (on your own)
Executive Committee Meeting (Riverside Boardroom)

1:30–3:00 ***Symposium: Predicting the future with memory-guided sensory codes***

– **John McGann, Czarnecki LA, Kass MD, Fast CD, & Rosenthal MC** *Rutgers*: Learning and expectation shape olfactory input to the mouse brain

– **Alfredo Fontanini** *Stony Brook*: Anticipatory activity in the gustatory cortex of alert rodents

– **Morrison FG, Dias BG, Kerry J. Ressler** *Emory*: Structural, functional and epigenetic responses to olfactory fear conditioning in mice

The Society thanks Elsevier for a generous contribution in support of the Poster Travel Award.

– **Kasia Bieszczad** *Rutgers*: Explaining Pavlov's sub-zero extinction with auditory cortical codes for memory

3:00–3:20 Coffee Break

3:20–3:45 **Nicola Grissom** *U Minnesota*: Male-specific deficits in reward learning in mouse models of autism

3:45–5:15 ***Symposium: Actions and habits in the rodent and human brain***

– **Kate Wassum** *UCLA*: A molecular brake on habit

– **Elizabeth Tricomi** *Rutgers*: Striatal influences on the motivational control of human behavior

– **Michael Shiflett** *Rutgers*: Action Control Deficits in Rodent Models of Psychiatric Disorders

– **Nathaniel Daw** *Princeton*: A computational view on actions and habits

5:30–7:30 Posters and Cash Bar
Hudson I, II, III

Saturday (Oct 1)

7:30–8:25 Breakfast
Hudson Hallway
Sessions in Hudson IV, V, VI

8:25–8:30 Welcome: **Andy Delamater** *Brooklyn-CUNY*

8:30 - 9:50 ***Talks: Aversive Learning***

– **Christopher Cain** *NYU Medical Center, Nathan Kline Institute*: Outcome-dependent vs. Habitual Active Avoidance

– **Moscarello J** *NYU*: Investigating the associative structure of active avoidance memory

– **Vinn Campese** *NYU*: Using Aversive Pavlovian to Instrumental Transfer to Identify Enduring Mechanisms of Control

– **Andy Poulos** *U Albany*: The Developmental Progression of Contextual Fear Conditioning and its Underlying Neuroanatomical Pathways

9:50–10:15 **Regina Sullivan** *NYU Medical Center, Nathan Kline Institute*: Learned maternal cues modify sensory processing and learning

10:15–10:35 Coffee

10:35–12:05 ***Symposium: Interval Timing***

– **Matell MS, De Corte BJ, Della Valle RB** *Villanova*: Attribution of a common cause for shifts in reinforcement intervals

– **Catalin Buhusi, Oprisan AS, Buhusi MC** *Utah State*: Clocks within Clocks: Timing by Coincidence Detection

– **Doyère V** *Paris-Saclay Institute of Neuroscience (Neuro-PSI)*: Timing the CS-US interval: A role for the Amygdala?

– **Narayanan NS, Emmons EB, DeCorte B, Kim Y** *U Iowa*: Ramping neurons in corticostriatal neuronal ensembles during interval timing

12:05–1:40 Lunch — Women in Learning satellite meeting at Greene Hooke
See last page of Program

1:40–2:50 ***Symposium: Cerebellar Learning Circuits***

– **Michael Mauk**indexMauk M *U Texas*

– **John Freeman, & Farley SJ** *U Iowa*: Amygdala Modulation of Cerebellar Learning

– **Hesslow G, Jirenhed DA, Johansson F, Rasmussen A** *Lund*: Temporal memory in cerebellar Purkinje cells

2:50–3:20 ***Past-President Lecture***

Matt Lattal *OHSU*: The baseline problem in associative and neurobiological studies of learning

3:20–3:40 Coffee

3:40–5:10 ***Symposium: Dopamine, associative learning, and changes in addiction***

– **Ostlund SB** *UC Irvine*: Dopamine and the transfer of motivational control over cue-triggered cocaine seeking

– **Burton AC, Bissonette GB, Zhao AC, Patel PK & Roesch MR** *U Maryland*: Prior cocaine self-administration increases action-outcome encoding in dorsal lateral striatum

– **Saddoris MP** *U Colorado*: Getting shell-acked: Critical differences in phasic dopamine signaling in the nucleus accumbens subregions during associative learning in normal and cocaine-experienced rats

– **Schoenbaum G** *NIDA*: Artificial dopamine transients are sufficient to unblock model-based learning in a preconditioning task

5:30–7:30 Posters and Cash Bar
Hudson I, II, III

7:30–9:00 Banquet
Hudson IV, V, VI
Speaker: **Mark Hauber** *Hunter-CUNY*: ***Self-referenced learning in avian host-parasite recognition systems***
Awards

Posters

Generally alphabetical by author except for some moved between days.

Posters whose first author's last name begins with A–L will be presented at Friday's Poster Session.

1 Acevedo K, Stein N, Breunig E, Ryckman A, & Bauer EP *Barnard* Extended amygdala circuits recruited by the expression of contextual fear conditioning

2 Adkins JM, Lynch JF, & Jasnow AM *Kent State* Estradiol Sex-Dependently Influences Contextual Fear Generalization in Rats

3 Alarcon DE & Delamater AR *Brooklyn-CUNY* The effect of extinction on the specific and general Pavlovian-to-instrumental transfer (PIT) effect.

4 Allen MT *Northern Colorado* Physical Exercise Slows Rather Than Enhances Classical Eyeblink Conditioning in Humans

5 Anderson LC & Petrovich GD *Boston College* DREADD activation of medial prefrontal cortex neurons induces renewal of Pavlovian conditioned responding to food cues in female rats

6 Aubry A, Schafe G, & Burghardt NS *Hunter College, CUNY* Chronic social defeat stress enhances the consolidation of a conditioned fear memory

7 Avcu P, Sinha S, Pang KCH, & Servatius RJ *Rutgers* Impaired active avoidance coping in male, but not in female rats after mild traumatic brain injury (mTBI)

8 Boulanger Bertolus J, Parrot S, & Mouly A-M *CRNL* Role of the dorsal striatum in encoding time interval durations in odor fear conditioning

9 Briones MA, Khandaker H, Seenauth A, Robinson RT, Galbraith D, & Schafe GE *CUNY* Intra-Amygdala Infusion of Curcumin Impairs Reconsolidation of a Pavlovian Fear Memory

10 Buhusi M, Olsen K, & Buhusi CV *Utah State* Temporal Discounting in a Model of Aging-related Parkinsonism

11 Bustamante J, Üngör M, & Lachnit H *U Chile* Reminder Cues Modulate Response Recovery in a Predictive Learning Task

12 Childs JE, DeLeon J, Su E, & Kroener S *UT Dallas* Vagus nerve stimulation reduces reinstatement to cocaine-seeking in a self-administration model of drug use

13 Colon LM, Santarelli A, Odynocki N, Poulos AM *U Albany* Retention of long-term context fear memories across development in female and male Long Evans rats

14 Czarnecki LA, Moberly AH, Fast CD, & McGann JP *Rutgers* Violating learned expectations shapes sensory input to the brain

15 de Solis CA, Ho A, Holehonnur R, & Ploski JE *UT Dallas* The Development of a Viral Mediated CRISPR/Cas9 System with Doxycycline Dependent gRNA Expression for Inducible In vitro and In vivo Genome Editing in the Amygdala

16 DeAngeli NE, Jiang MY, Bucci DJ, & Todd TP *Dartmouth* Intact renewal after extinction of conditioned suppression with lesions of either the retrosplenial cortex or dorsal hippocampus.

17 Della Valle RB, & Matell, MS *U Delaware* Spontaneously hypertensive rats show differences in temporal perception and task acquisition in a peak interval procedure

18 Do Carmo-Blanco N & Jozefowiez J *Charles de Gaulle Lille* Attentional load might explain the superiority of spaced over massed trial spacing in human contingency learning

19 Driskill C, Duzdabian H, Phensy AJ, & Kroener S *UT Dallas* N-acetyl cysteine treatment prevents behavioral deficits in an NMDA receptor dysfunction model of schizophrenia

20 Dutta S, Gilman TL, Cecil C, Adkins JM, & Jasnow AM *Kent State* Thy1 Neuron Activation in the BLA Promotes Fear Inhibition and Reduces Defeat-Induced Social Inhibition

21 Eddy MC, Todd TP, DeAngeli NE, Huszár R, & Bucci DJ *Dartmouth* Retrosplenial cortex lesions produce retrograde and anterograde context amnesia following overtraining

22 Ely SL & Wilson WJ *Albion* The Effects of MK-801 on Escape Behavior in the Earthworm, Lumbricus terrestris

23 Farley SJ & Freeman JH *U Iowa* Reversible Inactivation of Amygdala Central Nucleus Impairs Delay Eyeblink Conditioning with a Visual Conditioned Stimulus

24 Foilb AR, Flyer-Adams JG, Maier SF, & Christianson JP *Boston College* Posterior insular cortex is necessary for conditioned inhibition of fear, but not fear discrimination.

25 Giustino TF, Seemann JR, Acca GM, Goode TD, Fitzgerald PJ, & Maren S *Texas A&M* Beta noradrenergic blockade in the basolateral amygdala, but not the medial prefrontal cortex, rescues the immediate extinction deficit

26 Goode TD, Acca GM, & Maren S *Texas A&M* Reversible inactivation of the bed nucleus of the stria terminalis disrupts the expression of fear to unpredictable conditioned threats

27 Handy JD, Avcu P, Ko N, Ortiz A, Liberzon I, Marx C, Doria M, & Servatius RJ *Rutgers* Facilitated Acquisition of the Conditioned Eyeblink Response in Active Duty

Military Expressing Type D Personality and BI Temperament

28 Huckleberry KA, Copeland T, Shue F, Yin W, Chitwood RA, & Drew MR *U Texas* Optogenetic dissection of the contribution of dorsal and ventral adult-born neurons to context fear conditioning

29 Hui MH, Zelikowsky M, & Anderson DJ *CalTech* Chronic stress alters fear behavior in a neuromodulator-dependent manner

30 Kass MD, Rosenthal MC, & McGann JP *Rutgers* Plasticity of olfactory bulb interneurons after fear conditioning parallels the stimulus specificity of learning

31 Keiflin R, & Janak PH *Johns Hopkins* Phasic Activation of Ventral Tegmental Dopamine Neurons Mimics Reward Prediction Error and Promotes Model-Based Learning

32 Kennedy E, Campolattaro MM, & Lipatova O *Christopher Newport* The Impact of Fornix Lesions on Place Learning in the Open Field Tower Maze

33 Kirry AJ, Herbst MR, Poirier SE, Maskeri MM, Twining RC, & Gilmartin MR *Marquette* Sex-specific modulation of trace fear learning, but not working memory, by pituitary adenylyl-cyclase activating-polypeptide (PACAP) signaling in the prefrontal cortex.

34 Krasne FB[1], Bernier B[2], & Drew M[2] [1]*UCLA,* [2]*U Texas* The dentate gyrus is important to both encoding and recall of hippocampal representations

35 Kutlu MG, Connor D, Tumolo JM, Garrett B, & Gould TJ *Penn State* Nicotinic acetylcholine receptors modulate contextual fear extinction through ventral hippocampal GABAergic signaling

36 Laborda MA, Mallea J, & Miguez G *U Chile* Inhibitory potential of the extinction context is impaired by context exposure after but not during extinction training

37 Lacagnina AF, Wright AJ, Ayoub A, Denny CA, & Drew MR *U Texas* Spaced context exposure enhances context fear memory and hippocampal context coding

38 Lamoureux JA, & Simard, AA *Boston College* The Effects of Extinction and Counterconditioning on Negative Evaluative Conditioning in the Picture-Picture Paradigm

39 Latsko ML, & Jasnow AJ *Kent State* Deficits in adult social behavior caused by periadolescent social defeat are ameliorated by corticosterone.

40 López-García P, & Sánchez-Carrasco L *UNAM* Is resurgence affected by the reinforcement context?

41 Gallegos M, & Sánchez-Carrasco L *UNAM* Inhibitory associations Context-Response delay the reacquisition of instrumental responding on ABA renewal design.

42 Lynch III JF, Grissom NM, McKee SE, Schoch H, Walsh L, Marini M, Nickl-Jockschat T, Reyes TM, & Abel T *U Penn* Deficits in goal-directed learning are common to multiple mouse models of autism

43 Shipman ML, Trask S, Bouton ME, & Green JT *U Vermont* The prelimbic cortex attenuates responding of undertrained but not overtrained actions

44 Regetz TK, Miller DP, Nilles KL, Cook-Snyder DR, & Servatius RJ *Carthage* Partial reinforcement during signaled lever-press avoidance training is less detrimental to learning in behaviorally inhibited Wistar-Kyoto rats compared to Sprague Dawley rats

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The following posters (first author's last name begins with M–Y) will be presented at Saturday's Poster Session.

1 De Corte BJ, Matell MS, & Narayanan NS *U Iowa* Investigating how input to and output from the striatum mediates interval timing

2 Freestone DM, & Myers KP *Bucknell* The effects of habitual sugar consumption on interval timing in rats.

3 Lupkin SM, Lerner I, Sinha N, Tsai A, & Gluck MA *Rutgers* Trait-like variations in rapid-eye-movement sleep modulate hippocampus-amygdala connectivity during fear conditioning

4 Marton TM, Cavanaugh AR, Jin M, Ottenheimer D, & Hussain Shuler MJ *Johns Hopkins* The cost of time: Background reward rate affects temporal decision making.

5 Miguez G, Alfaro F, Canete A, Mallea J, & Laborda MA *U Chile* Assessing Retrospective Revaluation of the Blocking of Occasion Setter

6 Monk KJ, Dzaringa B, & Hussain Shuler MG *Johns Hopkins* The role of inhibition in cortical representations of cued temporal intervals

7 Navarro VM, Wasserman EA, McMurray B, & Roembke, TC *U Iowa* The role of negative associations in learning rich associative networks

8 Nelson JB[1], & Lamoureux JA[2] [1]*U Basque Country;* [2]*Boston College* The effects of extinction on context conditioning

9 Nentwig TB & Freestone DM *Bucknell* (Mis)estimating the Fixed Interval Gradient

10 Ng K, Pollock M, Urbanczyk P, Woon E, & Sangha S *Purdue* D1 receptor mediated signaling in the basolateral amygdala modulates safety-fear-reward cue discrimination

11 Woon E, Urbanczyk P, Pollock M, Ng K, & Sangha S *Purdue* Prior trauma impairs safety-fear-reward cue discrimination

12 Noble LJ, Meruva VB, Kilgard MP, & McIntyre CK *UT Dallas* Vagus nerve stimulation reverses extinction impairments and alters PTSD symptoms in the SPS animal model

13 Opendak MM, Wood K, Mansour R, Serrano P, & Sullivan RM *NYU* Amygdala PKMζ increases with the emergence of fear learning in infant rats

14 Ortiz S, Gilman TL, Cecil C, Immel ZJ, Adkins S, Huda R, Adkins JM, & Jasnow AM *Kent State* Glutamatergic signaling in the nucleus accumbens modulates cued fear extinction

15 Palmisano AN, Hudd E, McQuade C, de Wit H, &

Astur RS *U Connecticut* Nicotine enhances responding for chocolate rewards

16 Parrish JN[1], Lam SY[1], Speth RC[2], & Torregrossa MM[1] [1]*U Pittsburgh;* [2]*Dept. of Pharmaceutical Sciences, Nova Southeastern University, Fort Lauderdale, FL* Estradiol modulation of the renin angiotensin system and the regulation of fear extinction

17 Payne JW, Opara V, Petrov P, & Iordanova MD *Concordia* The effects of a mixed extinction paradigm on the retrieval of previously reinforced Pavlovian associations

18 Polack CW, O'Hara S, & Miller RR *Binghamton* Associative structure of inhibitory perceptual learning

19 Pollack GA, & Bergstrom HC *Vassar* Cued fear memory retrieval accuracy over time

20 Robinson-Drummer PA, Heroux NA, & Stanton ME *U Delaware* Intra-medial prefrontal cortex antagonism of muscarinic acetylcholine receptors disrupts the context preexposure facilitation effect

21 Rosenthal MC, Bacallao M, Kessler EM, & McGann JP *Rutgers* Discriminative Olfactory Aversive Learning Induces Rapid Physiological and Perceptual Plasticity

22 Russo AS, & Parsons RG *Stonybrook* Acoustic startle response as a predictive index of a PTSD-like phenotype in rats

23 Voulo ME, & Parsons RG *Stonybrook* Response-specific sex difference in the retention of fear extinction

24 Heroux NA, Buban KN, Robinson-Drummer PA, Rosen JB, & Stanton ME *U Delaware* Inactivation of the medial prefrontal cortex (mPFC) impairs the retention of a context-shock association in the CPFE but not sCFC

25 Sanders HR, & Stanton ME *U Delaware* Preweanling rats can acquire, but not retain contextual associations in object-in-context and contextual fear conditioning paradigms.

26 Schepers ST, & Bouton ME *U Vermont* Renewal in the Context of Stress: A Potential Mechanism for Stress-induced Reinstatement.

27 Shang A, Bylipudi S, & Bieszczad KM *Rutgers* Epigenetic mechanisms dynamically facilitate learning in an auditory discrimination task

28 Sharp JL, Miller ME, Fountain SB, & Riccio DC *Kent State* Adolescent methylphenidate exposure causes sex-specific differences in adult rat serial pattern retention

29 Sheynin J, Baidya S, & Liberzon I *U Michigan* Acquisition and generalization of avoidance: A mismatch between expectancy and behavior

30 Sheynin J, Shind C, Ebanks-Williams Y, Beck KD, & Myers CE *U Michigan* Greater avoidance behavior in individuals with symptoms of posttraumatic stress disorder (PTSD)

31 Shors TJ, Millon EM, Chang HYM, Olson RL, & Alderman BL *Rutgers* Do Sex Differences in Rumination Explain Sex Differences in Depression?

32 Sinha N, Mattfeld AT, & Gluck MA *Rutgers* Dopamergic modulation of reward learning across the lifespan

33 Sullivan RM, Opendak M, & Wilson D *Nathan Kline Institute-NYU* Learned maternal cues modify sensory processing and learning

34 Tallot L, Diaz-Mataix L, Graupner M, & Doyère V *CNRS* Interactions in an amygdalo-prefronto-striatal circuit for processing the CS-US interval

35 Thrailkill EA, Rojas G, & Bouton ME *U Vermont* How to Break a Habit

36 Trask S, & Bouton ME *U Vermont* Reducing the negative impact of context change on an operant response

37 Travaglia A, Bisaz R, Sweet ES, Blitzer RD, & Alberini CM *NYU* Latent infantile memories and critical period mechanisms

38 Tumolo JM, Kutlu MG, & Gould TJ *Penn State* Chronic nicotine alters spontaneous recovery of contextual fear differentially in male and female mice

39 Whitlow, JW *Rutgers* Nature of the Outcomes and Configural Learning

40 Ye X, Kapeller-Libermann D, Travaglia A, & Alberini CM *NYU* Prefrontal circuit and synaptic mechanisms underlying retrieval-mediated fear memory enhancement and extinction suppression

41 Barone J, Ludwig RJ, & Welch MG *Columbia U Medical Center* Calming Cycle theory and Pavlov's effect of person

42 Johnson BJ, & Wilson WJ *Albion* Cross-Species Comparison of Response to Light in Earthworms

43 Zanca RM[1,3], Caamano-Tubio R[2], Avila JA[1,3], Serrano PA[1,3], & Delamater AR[2,3] [1]*Hunter College - CUNY;* [2]*Brooklyn College - CUNY;* [3]*Graduate Center of CUNY* The Role of GluA1 and GluA3 trafficking during Pavlovian Reward Conditioning and Extinction

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Abstracts

Listed in alphabetical order by first author's last name. Abstracts are not indexed.

Acevedo K, Stein N, Breunig E, Ryckman A, & Bauer EP *Barnard*

Extended amygdala circuits recruited by the expression of contextual fear conditioning The bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala (CE) are reciprocally connected and share similar cell types and efferent targets. It has been suggested that they might coordinate their activity and/or function in parallel to regulate fear-like and anxiety-like behaviors. Here, we characterized the activity of neurons within the anterolateral portion of the BNST which project to the CE in response to the expression of contextual fear conditioning. As the BNST is

one of the few sexually dimorphic structures in the rodent brain, we used both male and female Sprague Dawley rats. Animals received infusions of the retrograde tracer Fluoro-Gold into the CE 5-6 days before undergoing contextual fear conditioning with 3 unpaired footshock USs. 24 hours later, they were placed in the conditioning chamber for 10 min, perfused 45 min later, and their brains processed using standard immunohistochemical techniques. While there was no difference in the percentage of time spent freezing to the context in male and female rats, only male rats showed significant upregulation of the immediate early gene Arc in the anterolateral BNST, compared to rats receiving no footshocks on training day. In both male and female rats, the majority of Arc+ neurons expressed corticotropin releasing factor (CRF). We then characterized the neurons within the BNST which project to the CE by analyzing Fluoro-Gold+ neurons. We confined our analysis to the anterolateral BNST. Slightly less than half of the Fluoro-Gold+ neurons were Arc+ following the expression of context fear conditioning, but the majority were CRF+ in both male and female rats. These studies highlight the important role for CRF containing neurons within the BNST in the expression of contextual fear conditioning. They also suggest that only a subset of CE-projecting cells within the BNST are active during contextual fear expression. *Barnard Summer Research Institute, Sherman Fairchild Foundation, NIH grant: 1R15MH107008*

Adkins JM, Lynch JF, & Jasnow AM *Kent State*
Estradiol Sex-Dependently Influences Contextual Fear Generalization in Rats Generalized fear occurs when animals, including humans, exhibit fear to non-fearful cues or contexts. Generalized fear is a shared characteristic of several anxiety disorders in humans, many of which afflict women more so than men. Our recent work has demonstrated that, in gonadectomized rats, estradiol induces contextual fear generalization in females but reduces fear generalization in males. We have found that the enhanced generalization observed in females is mediated through activation of estrogen receptor-β (ERβ), but not ERβ, specifically in the dorsal CA1 region of the hippocampus (dCA1). In contrast, both ERα and ERβ mediate the reduced fear generalization observed in male rats, but the specific brain regions at which estradiol acts to produce this effect remain unidentified. Given the influence estradiol has on glutamate receptors, we hypothesized estradiol induces generalization in female rats by enhancing glutamatergic signaling within the ACC and the hippocampus. Using a passive avoidance paradigm, we examined the effects of low doses of NMDA or AMPA receptor antagonists (to avoid affecting memory of the training context) infused into the dorsal CA1 of the hippocampus or the anterior cingulate cortex (ACC) of gonadectomized females receiving estradiol. Our results suggest that both AMPA and NMDA receptors are necessary for estradiol-induced fear generalization. In addition to evaluating the role of glutamate signaling in estradiol-facilitated fear generalization in females, we also sought to pinpoint specific brain regions involved in the estradiol-reduced fear generalization in males. Passive avoidance testing in gonadectomized male rats revealed that estradiol infusions into the bed nucleus of the stria terminals (BNST) resulted in significant fear generalization, suggesting that estradiol does not act at the BNST to reduce generalization in males. Upcoming experiments will target the dorsal CA1 region of the hippocampus and the medial amygdala, as these regions along with the BNST have high aromatase and ER expression in male rats. Understanding the mechanisms behind the sex-dependent behavioral responses to estradiol and how it influences fear generalization will be useful in facilitating development of sex-specific therapeutics for multiple anxiety disorders.

Alarcon DE & Delamater AR *Brooklyn-CUNY*
The effect of extinction on the specific and general Pavlovian-to-instrumental transfer (PIT) effect. Presentations of a conditioned stimulus (CS) can increase instrumental performance, phenomenon known as Pavlovian-to-instrumental transfer (PIT) effect. This effect can take two distinct forms: the general and the specific PIT effects. In the general PIT, a CS presentation elevates responses trained with an outcome from the same motivational valence of that predicted by the CS. But in the specific PIT effect, the CS elevates responding only if the CS and the response were trained with the same outcome. It has been observed that extinction procedures aiming to weaken the association between the CS and the outcome do not affect the specific form of PIT (Delamater, 1996), but no comparable study has been conducted on its general form. As research on the neural mechanisms involved in PIT indicate that both forms are governed by different brain regions (Corbit & Balleine, 2005; 2011), it is possible that extinction treatments affect both forms of PIT differentially. Two experiments were conducted to assess the effect of extinction on the specific and general PIT effect. Rats were trained to perform one response to obtain one outcome (R1->O1). Then one CS was paired with the delivery of the same outcome as the response, and another with a different outcome (CS1->O1, CS2->O2). In addition, two CSs were not reinforced (CS3-, CS4-). In Experiment 1, the outcomes were delivered across the CS presentations, while in Experiment 2 only after the onset of the CS. In both experiments half of the subjects received non-reinforced presentations of the CSs (extinction), and the other half received context exposure. In the subsequent PIT test, all subjects performed the instrumental response in the presence and absence of the CSs. The PIT tests of both experiments revealed that extinction resulted in an increased specific and general PIT effect, relative to the group that only received context exposure. These results suggest that both forms of PIT are highly resistant to extinction, and that extinction might enhance this effect presumably by reducing competing goal

tracking CRs. *NIDA SC1DA034995*

Allen MT *Norhtern Colorado*
Physical Exercise Slows Rather Than Enhances Classical Eyeblink Conditioning in Humans The benefits of exercise for neural function are well known. A study in male rats found that physical exercise improves eyeblink conditioning to paired CS tone and US eye shock trials (Green et al., 2011). There were no exercise effects on pseudo-conditioning. The current study was conducted to determine if exercise also enhances eyeblink conditioning in humans. In this preliminary study, we used self-report of normal exercise habits to group our participants as high or low exercise as well as a sample that included both males and females. We hypothesized that participants self-reporting higher levels of weekly exercise would exhibit enhanced acquisition of conditioned eyeblink, but no differences in response to unpaired CS and US trials. We also hypothesized that females would exhibit better eyeblink conditioning than males. Sixty seven undergraduates (14 males and 53 females) voluntarily participated for research credit. All participants completed a questionnaire about their exercise habits. Participants were grouped as low exercise (one hour or less per week) or high exercise (3 or more hours per week). Thirty participants in the acquisition condition received 6 blocks of ten trials each of which consisted of 8 paired trials with a 500 ms tone CS which overlapped and co-terminated with a 50 ms, 5 psi corneal air puff US along with a US alone trial and a CS alone trial. Thirty seven participants in the pseudo-conditioning control condition received 60 pseudo-randomly presented CS alone and US alone trials. Pseudo-conditioning resulted in no significant increase in eyeblinks to the tone. There was a decrease in UR amplitude across US alone trials in the pseudo-conditioning in both high and low exercise individuals. Low exercise participants exhibited enhanced CR acquisition as compared to high exercise participants. Females also exhibited enhanced CR acquisition as compared to males. There were no exercise or gender differences in UR amplitude on US alone test trials across six blocks of acquisition training. Surprisingly, exercise had the opposite effect on human eyeblink conditioning as was previously reported in male rats. Possible differences in exercise effects in rats and humans may be due to methodological differences in eyeblink conditioning between rats and humans as well as gender effects. Known alterations of hippocampal and cerebellar substrates by exercise, anxiety and stress will be discussed as possible causes for the deficits in eyeblink conditioning in humans.

Anderson LC & Petrovich GD *Boston College*
DREADD activation of medial prefrontal cortex neurons induces renewal of Pavlovian conditioned responding to food cues in female rats Renewal of responding to food cues after extinction may explain the inability to resist palatable foods and change maladaptive eating habits. Recently, we found sex differences in context-dependent renewal of responding to extinguished Pavlovian food cues and differential recruitment within the ventromedial prefrontal cortex (vmPFC). Male rats exhibited renewal of responding and had higher Fos induction within the vmPFC compared to a control group, while females failed to show renewal of responding and had lower Fos induction within the vmPFC compared to a control group. Here, we used DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) to examine whether stimulating the vmPFC during renewal could induce cue-specific responding in females. Female, Long-Evans rats received bilateral stereotaxic injections into the vmPFC of a viral vector containing the gene for a synthetic stimulatory G-protein-coupled receptor (AAV5-hSyn-HA-hM3D-IRES-mCitrine) or a control viral vector (AAV5-hSyn-EGFP). After recovery rats were trained to associate a tone (conditioned stimulus, CS) with food (unconditioned stimulus in Context A. Acquisition was followed by extinction sessions with CS-only presentations in Context B. Rats were tested for renewal of responding with CS-only presentations in Context A and Context B, counterbalanced for order, on separate days. 30 minutes prior to each test, rats were injected with clozapine N-oxide (CNO, 3mg/kg, i.p.) or vehicle. Rats either received CNO on both days or vehicle on both days, resulting in 3 groups: DREADD+CNO, DREAD+Vehicle, and Control Virus+CNO. The measure of learning was an increase in the expression of food cup behavior (conditioned response, CR) during CSs, expressed as an elevation score (baseline responding subtracted). Renewal of responding was determined by higher elevation scores in the acquisition context (Context A) compared to the extinction context (Context B). Preliminary results suggest renewal of responding to the CS in the DREADD+CNO group (higher CRs in Context A compared to B) compared to the other two groups, which showed similar responding in both contexts. These results suggest the vmPFC activation is critical during renewal of responding to food cues and a site of sex differences. *Research was supported by NIH Grant R01DK085721*

Aubry A, Schafe G, & Burghardt NS *Hunter College, CUNY*
Chronic social defeat stress enhances the consolidation of a conditioned fear memory Exposure to chronic stress is a major risk factor for developing numerous psychiatric disorders. An increasingly popular method for studying the effects of stress on the brain is to expose subjects to social defeat stress, an ecologically valid model of social stress that reliably induces depressive- and anxiety-like behavior in mice. However, it is not known how social defeat affects other aspects of stress-related disorders, such as changes in emotional learning. We tested the effects of ten days of social defeat stress on social interaction and auditory fear conditioning. During social defeat stress, an intruder 129Sv/Ev mouse was placed into the home cage of a larger CD-1 mouse prescreened for aggressive behavior. The two mice interacted

for 5 minutes, during which time the CD-1 mouse attacked the intruder mouse. The two mice were then housed together in the same cage for approximately 24 hours, separated by a perforated Plexiglas divider that prevented further physical contact but allowed for continuous psychological stress from sensory cues. Control mice were pair housed with one 129/SvEv mouse on each side of the perforated divider and were never in contact with a CD-1 mouse. Social interaction was tested one day after the final defeat session. Six days later, mice were fear conditioned with 3 tones (20s, 2kHz, 70dB) that co-terminated with a foot shock (2s, 0.75mA). Short-term memory was tested one hour later with 3 tone presentations and long-term memory was tested the next day with 5 tones. We found that stressed mice spent less time interacting with the CD-1 than non-defeated control mice, which is consistent with the known effects of social defeat stress on social avoidance. Interestingly, stress-induced social avoidance was generalized to mice of the same strain (129Sv/Ev). While there were no effects of stress on acquisition, shock sensitivity, or short-term memory, stressed mice froze significantly more to the tone during the long-term memory test, indicating that stress increased memory consolidation. Additional experiments are in progress to identify the neural correlates of this stress-induced increase in fear memory in the amygdala. *This work was supported by the RCMI-funded Center for Translational and Basic Research at Hunter College (NIMHD #MD007599), the National Institute on Minority Health and Health Disparities of the National Institutes of Health (G12MD007599) and by a CUNY Dean K. Harrison Fellowship.*

Avcu P, Sinha S, Pang KCH, & Servatius RJ *Rutgers*
Impaired active avoidance coping in male, but not in female rats after mild traumatic brain injury (mTBI) Mild traumatic brain injury (mTBI) is presumed to increase risk for the development of post-traumatic stress disorder (PTSD) as well as depression in civilians. PTSD is conceptualized as an interaction of inherent risk and trauma to induce sequelae conforming to re-experiencing, avoidance, negative cognitions and mood, and hyper-arousal. In sharp contrast to PTSD, we consistently find profoundly and persistently attenuated acoustic startle responses (ASRs) after mTBI in male rats. However, the effects of mTBI are not yet known for female rats. Here, we examined ASRs and two processes that underlie avoidance learning in male and female rats; an inherent ability to acquire cue-outcome associations (classical conditioning) and response-outcome associations (instrumental conditioning). In Experiment 1, the ability to acquire cue-outcome associations was assessed through classical conditioning of eyeblink responses after mTBI. In Experiment 2, avoidance was assessed in lever-press escape/avoidance paradigm; wherein rats learn to lever-press to limit shock exposure (escape), and to prevent shock exposure all together (avoidance). In this paradigm, while excessive expression of avoidance is associated with anxiety, its reduced expression found in model of depression. Finally, efficient stress coping is expressed as a balance of escape and avoidance. In both experiments, the ASR data replicated the previous findings in males and extended to females; post-injury ASRs were attenuated and did not show a sign of recovery until post-injury day 42 in both male and female rats. Simple associative learning and escape responding were unaffected after mTBI in both sexes. However, avoidance learning was selectively impaired in male mTBI rats, but not in female mTBI rats. Together, the study showed that mTBI produces behavioral abnormalities that are inconsistent with signs associated with PTSD, but more conducive to depression. Sex-specific differences in avoidance support a neuro-organic basis for depression in the aftermath of mTBI, which can help to determine intervention techniques, aimed at improving adaptive coping following mTBI. *VA Merit Grant: I01 BX000132; NIH Grant: NS044373; and NJ Commission on Brain Injury Research: CBIR11PJT003 and CBIR14FEL014*

Barone J, Ludwig RJ, & Welch MG *Columbia U Medical Center*
Calming Cycle theory and Pavlov's effect of person Results from a randomized controlled trial of Family Nurture Intervention (FNI) among prematurely born infants showed significantly improved maternal behaviors and infant neurodevelopment and behavior through 18 months, including a significantly reduced risk for autism. Preliminary results from a pilot study of FNI in preschool children found significant reduction in adverse behavior. Calming cycle theory proposes that FNI shapes early emotional behavior via subcortical visceral/autonomic co-conditioning between mother and infant. Two new constructs, emotional connection and visceral/autonomic co-regulation, are defined within a functional Pavlovian conditioning framework and are theorized to be part of an evolutionarily conserved mammalian phenomenon first identified by Pavlov as effect of person. Pavlov's disciple, W. Horsley Gantt, spent much of his life trying to convince the fields of psychology and psychiatry that the roots of neurosis and emotional behavior are connected to the phenomenon. According to Calming Cycle theory, the baby and mother establish an emotional connection and visceral/autonomic co-regulation in utero during gestation via a Pavlovian conditioning mechanism. After normal birth, sensory stimulation and emotional communication triggers an autonomic reflex that calms and attracts the two to one another. Visceral/autonomic co-regulation is thought to account for the observed soothing effects that mother and infant have on one another after FNI. Calming cycle theory contains several theoretical and practical advances. The theory provides a novel subcortical-physiological explanation for early mother/infant emotional behavior. It advances functional Pavlovian conditioning theory by adding the concepts of co-conditioning and co-regulation and applying them to

the gestational and perinatal period. It provides new constructs of emotional connection and visceral/autonomic coregulation that describe early mother-infant interactions and behavior. It advances vagal theory by providing a subcortical visceral/autonomic conditioning mechanism to account for approach and avoidance behavior. Finally, the calming cycle is embedded in a practicable intervention in which the mechanism can be tested. *This work is supported by the Einhorn Family Charitable Trust*

Bieszczad KM *Rutgers*
Explaining Pavlov's sub-zero extinction with auditory cortical codes for memory Memories have content. They constitute the storage of select details of experienceâĂŤwhich can be as multisensory and specific as the experiences that produce them. This characteristic requires that at least part of the neural âĂIJmemory traceâĂİ have the same capability for select sensory specificity. The central focus of this talk is to demonstrate a sensory cortical function for memory using the auditory cortex as a model. Acoustic information is represented as a tonal frequency (âĂIJtonotopicâĂİ) map in primary auditory cortex (A1), which specializes to represent sound. However, 40 years of research show incredible capacities throughout life for learning to induce plasticity in A1 tonotopy. What is this plasticity good for? The A1 map appears to encode the importance of relevant signal frequencies by enhancing the representation of a signal that has acquired behavioral significance: the more important the tonal frequency-cue during experience, the larger its cortical size of representation. Furthermore, a soundâĂŹs gain in A1 area is related to memory strength: the larger the area, the stronger the memory and the more likely the sound will cue and elicit behavior. Along this line of thinking, we know that many factors weaken memories. Memory is subject to degradation by forgetting and to suppression after time or interference. If weakly formed, as with non-arousing, insignificant experiences, large representations of sound-specific memories would not be established, making them more susceptible. Moreover, forgetting or extinction would have to degrade enlarged networks, which indeed has been shown to do so during auditory associative extinction. For instance, memories that withstand auditory associative extinction occur with the maintenance of A1 map expansions (Bieszczad & Weinberger 2012)âĂŤcortical representational expansion in A1 appears to make these auditory memories resistant to weakening. On the assumption that memories involve networks of functionally linked neurons, the greater the number of neurons taking part in strong memories could be reversed by manipulating the mechanisms that enabled expansion in the first place, or by enhancing A1 map retractions for specific sound cues by enabling extinction-dependent sensory cortical plasticity during extinction training. Such waxing and waning of A1 map representation over the course of experience shows that sensory cortical reorganization participates in memory by encoding a cueâĂŹs signal value for prediction. In so doing, we can show sound-specific behavioral and neural evidence of PavlovâĂŹs so-called âĂIJsubzeroâĂİ extinction. *NIDCD/NIH (R03DC014753-01)*

Boulanger Bertolus J, Parrot S, & Mouly A-M *CRNL*
Role of the dorsal striatum in encoding time interval durations in odor fear conditioning Time perception is crucial to survival and goal reaching and interval timing also guides fundamental animal behaviors. In pavlovian fear conditioning, an initially neutral stimulus (the conditioned stimulus, CS) predicts the arrival of an aversive unconditioned stimulus (generally a mild foot-shock, US) at a fixed time interval. The aim of the present study was to investigate the role of dorsal striatum (known to be involved in time processing) in timing interval durations in odor fear conditioning in rats. An experimental setup allowing the simultaneous recording of respiration, ultrasonic vocalizations and behavior during training (10 Odor-Shock pairings, with a 20s CS-US interval) enabled us to detect the emergence of temporal patterns in the animalâĂŹs fear response during acquisition, indicating that rats are able to encode CS/US interval duration after a few training trials. We previously showed that odor fear acquisition was associated with an increase in 2-deoxyglucose uptake in the dorsomedial striatum suggesting that this structure might be involved in encoding the odor-shock association and/or the temporal link between the two stimuli. In order to test this hypothesis, here we carried out transient inactivation of the dorsomedial striatum either before learning acquisition or before a shift in the learned CS/US interval duration, and measured the effects of this treatment on the temporal pattern of the behavioral response. The data suggest that a functional striatum favors the stability of a learned temporal pattern while its inactivation allows a more flexible temporal pattern. We then measured DA content in this region using intracerebral microdialysis during the acquisition session which included 7 odor-shock pairings, 6 with a 20s CS-US interval and the last one with a 30s interval. We observed a decrease in DA concentration at the onset of the pairings, which stabilized throughout the 6 trials with a 20s CS-US interval and a further decrease when the interval duration was shifted to 30s. Taken together the present data suggest that while the dorso-medial striatum is not involved in the formation of the odor-shock association per se, it might be involved in the production of a stable temporal pattern of fear behavioral response related to the duration of the CS-US interval.

Briones MA, Khandaker H, Seenauth A, Robinson RT, Galbraith D, & Schafe GE *CUNY*
Intra-Amygdala Infusion of Curcumin Impairs Reconsolidation of a Pavlovian Fear Memory Curcumin, a yellow-pigment compound found in the popular Indian spice turmeric (Curcuma longa), has been extensively investigated for its anti-inflammatory, neuroprotective, and chemopre-

ventative properties. Recently, we have shown that a dietary source of curcumin significantly impairs the reconsolidation of a Pavlovian fear memory, a widely studied animal model of traumatic memory formation in post-traumatic stress disorder (PTSD). Here, we examined the molecular and behavioral effects of direct intra-amygdala infusion of curcumin on the reconsolidation of a Pavlovian fear memory. Rats were first trained with 3 pairings of a 5 kHz, 75 dB, 30 sec tone conditioned stimulus (CS) that co-terminated with a 1 sec, 1.0 mA footshock (unconditioned stimulus; US). Twenty-four hours later, rats were given a reactivation trial (1 CS presentation) in a new context (Context B). One hour after the reactivation session, rats were given an infusion of curcumin (1 μg/side; 0.5 μl) or vehicle directly into the lateral amygdala (LA). Half of the rats were then sacrificed 30 mins later to examine retrieval-related expression of phosphorylated-IKK, histone acetylation, and the immediate early gene EGR-1 in the LA. The other half were tested for post-reactivation (PR) short-term memory (STM) 3 hrs later and PR long-term memory (LTM) 24 hrs later in Context B. Curcumin-infused rats exhibited significantly impaired retrieval-related expression of phosphorylated IKK-alpha, acetylated histone H3 (Lys 18), and the immediate early gene Egr-1 in the LA relative to vehicle controls. Further, we observed that intra-LA infusion of curcumin impaired reconsolidation of a fear memory; PR-LTM was significantly impaired, while PR-STM was intact. We observed no effect of intra-LA infusion curcumin on retention of the fear memory in non-reactivated rats or when curcumin was infused 6 hours following reactivation. Collectively, our findings indicate that direct infusion of curcumin into the LA is capable of impairing retrieval-related expression of memory-related proteins in the LA and the reconsolidation of a Pavlovian fear memory. Our findings are consistent with our dietary findings and add further support to the hypothesis that curcumin may be useful as an adjunct in the treatment of psychological disorders such as PTSD that are characterized by fearful memories. *This work was supported by the RCMI-funded Center for Translational and Basic Research at Hunter College (NIMHD #MD007599) and by the Hunter RCMI-RISE program.*

Buhusi M, Olsen K, & Buhusi CV *Utah State*
Temporal Discounting in a Model of Aging-related Parkinsonism Parkinson's Disease, the most common neurodegenerative movement disorder, is also associated with deficits in planning, working memory and inhibitory control, suggestive of frontal executive dysfunction due to alterations in dopaminergic circuits. Glial-derived neurotrophic factor (GDNF) is a trophic factor essential to the functional maintenance of dopaminergic neurons. A partial reduction of GDNF levels in GDNF heterozygous mice leads to an accelerated decline of dopamine and motor function, making these mice a model of aging-related Parkinsonism. We investigated decision making in adult, presymptomatic GDNF-heterozygous (HET) mice and their wild-type littermate controls (WT). Results failed to indicate deficits in decision making in adult, presymptomatic GDNF heterozygous mice, relative to their wild-type littermates. However, after mice were exposed to chronic unpredictable stress, GDNF heterozygous mice showed increased impulsive choice relative to littermate controls. As previous research identified noradrenergic agents that reduce impulsivity in the temporal discounting paradigm, we investigated whether these agents can rescue the deficits in impulse control in chronically-stressed GDNF heterozygous mice. Confirming previous results, these agents reduced impulsive choice in wild-type mice. However, they were unable to modulate temporal discounting in chronically-stressed GDNF HET mice, possibly as a result of developmental effects of GDNF deficiency on their decision-making circuits. Indeed, chronically-stressed GDNF heterozygous mice showed decreased neural activation in decision-making circuits relative to their wild-type littermates, suggestive of a maladaptive response to stress. These results identify chronically-stressed adult, presymptomatic GDNF-deficient mice as a double-hit (gene x environment) model of stress-related decision-making deficits. *NS090283*

Buhusi CV, Oprisan AS, Buhusi MC *Utah State*
Clocks within Clocks: Timing by Coincidence Detection The many existent models of timing rely on vastly different mechanisms to track temporal information. Here we examine these differences, and identify coincidence detection in its most general form as a common mechanism that many apparently different timing models share, as well as a common mechanism of biological circadian, millisecond and interval timing. This view predicts that timing by coincidence detection is a ubiquitous phenomenon at many biological levels, explains the reports of biological timing in many brain areas, explains the role of neural noise at different time scales at both biological and theoretical levels, and provides cohesion within the timing field. *MH073057, NSF-CAREER 1054914, NS090283*

Burton AC, Bissonette GB, Zhao AC, Patel PK & Roesch MR *U Maryland*
Prior cocaine self-administration increases action-outcome encoding in dorsal lateral striatum Dorsal lateral striatum (DLS) is a highly associative structure that encodes relationships between environmental stimuli, behavioral responses, and predicted outcomes. DLS is known to be disrupted after chronic drug abuse, however it remains unclear what neural signals in DLS are altered. Current theory suggests that drug use enhances stimuli-response processing at the expense of response-outcome encoding, but this has mostly been tested in simple behavioral tasks. Here, we ask what neural correlates in DLS are affected by previous cocaine exposure as rats perform a complex reward-guided decision-

making task where contingencies change often. We recorded from DLS after a month-long withdrawal period in cocaine-exposed rats as they performed a reward-guided decision-making task where predicted reward value was independently manipulated by changing the delay to or size of reward associated with response direction across a series of trial blocks. After cocaine self-administration, rats exhibited stronger biases toward higher value reward and firing in DLS more strongly represented action-outcome contingencies rather than outcomes predicted by selected actions (chosen-outcome contingencies) and associations between stimuli and actions (stimulus-response contingencies). These results suggest that cocaine self-administration strengthens action-outcome encoding in rats (as opposed to chosen-outcome or stimulus-response encoding), which abnormally biases behavior toward valued reward when there is a choice between two options during reward-guided decision-making. *R01DA031695, MR*

Bustamante J, Üngör M, & Lachnit H *U Chile*
Reminder Cues Modulate Response Recovery in a Predictive Learning Task In two experiments in a predictive learning task, participants received pairings of a target cue and an outcome in one context, preceded by presentations of a reminder cue. In a second phase, participants received extinction in a different context with the target cue preceded by a second, different reminder cue. Responding was tested in a third context with either the acquisition or the extinction cue preceding the test trials. Participants showed in both experiments stronger responding to the target when the acquisition reminder cue was presented compared to when the extinction reminder cue was presented, even after both reminder cues were equally followed by the outcome and its absence. This result suggests that the effect of the reminder cues was not based on a direct association between the reminder cues and the outcome.

Cain CK *NYU Medical Center, Nathan Kline Institute*
Outcome-dependent vs. Habitual Active Avoidance In the active avoidance paradigm, subjects learn to escape an aversive CS and prevent a painful US by emitting a specific avoidance response (AR; e.g. shuttling). Avoidance research stalled in the 1970s for several reasons. First, S-R learning theorists were unable to resolve disputes about the reinforcement mechanism. Some emphasized the escape contingency (âĂIJfear reductionâĂİ associated with CS-termination), some the avoidance contingency (US-omission) and still others suggested a key role for response-produced safety signals (feedback stimuli negatively correlated with the CS and US). Second, the avoidance paradigm caused problems for early neurobiologists studying defensive brain circuits. For instance, amygdala lesions were equally likely to impair, facilitate or have no effect on avoidance. Third, studies of Pavlovian conditioning supplanted avoidance after Bolles suggested that ARs were likely SSDRs guided by Pavlovian cues. Although appetitive conditioning researchers soon devised procedures like US-devaluation to differentiate between cognitive and reflexive instrumental behaviors, these strategies never took hold in avoidance, perhaps because the outcome in avoidance remained uncertain. In this talk I will discuss two lines of research investigating the outcome-dependence and amygdala-dependence of ARs in rats. Using a novel devaluation procedure, we found that counterconditioning of explicit response-produced safety signals impaired ARs after moderate training, but not after overtraining. This aligns with our lesion and c-Fos data suggesting that basolateral amygdala is required for avoidance early in training but not after overtraining. This pattern is reminiscent of results from appetitive instrumental conditioning, were responding transitions from outcome-dependent to habitual with overtraining, as brain circuits mediating behavior also shift. However, it is (largely) inconsistent with an SSDR view of avoidance, since Pavlovian reactions depend on BLA for the lifetime of the memory, even after overtraining.

Campese V, & LeDoux JE *NYU*
Using Aversive Pavlovian to Instrumental Transfer to Identify Enduring Mechanisms of Control A conditioned stimulus (CS: e.g., tone) that has been paired with an aversive unconditioned stimulus (US: e.g., footshock) produces freezing and other well-documented defensive behaviors. However, after acquisition of a response capable of controlling footshock delivery, presentation of the CS results in augmentation of avoidance performance instead, an effect known as Pavlovian to Instrumental Transfer (PIT). PIT offers a unique way of isolating changes in CS processing that occur as a result of avoidance learning. Previous reports from our lab show that an amygdala-based circuit underlies PIT and that this circuit diverges from that known to contribute to avoidance learning itself. Using chemogenetic and optogenetic approaches, recent studies weâĂŹve done have investigated which neural circuits beyond the amygdala are involved in PIT. Preliminary findings suggest that coordinated neuromodulatory processes are crucial. For example, while dopaminergic (DA) transmission is required, noradrenergic (NE) influences are suppressed during transfer. Providing evidence for a role of DA, chemogenetic inhibition of ventral tegmental area or nucleus accumbens both eliminated PIT and similar effects were seen with systemic treatment of the D1 antagonist SCH 23390. On the other hand, systemic NE beta-receptor agonism with procaterol and selective chemogenetic excitation of locus coeruleus terminals in central amygdala both eliminated PIT. The coordination of these neuromodulatory effects may depend on context-based processes promoting mediated generalization between signals for the footshock US. This possibility is currently being explored using behavioral and optogenetic manipulations targeting prefrontal cortex and hippocampus.

Childs JE, DeLeon J, Su E, & Kroener S *UT Dallas*

Vagus nerve stimulation reduces reinstatement to cocaine-seeking in a self-administration model of drug use Cocaine addiction can cause maladaptive neuroplasticity that persists long after cessation of drug taking. The permanence of cue associations formed during drug taking contributes to the difficulties in treating addiction, because re-exposure to these cues can trigger relapse to drug use. Breaking the cue/drug association via extinction learning is one approach to preventing relapse. We have previously shown that vagus nerve stimulation (VNS) can enhance extinction of conditioned fear and alters neural plasticity in fronto-limbic circuits that govern extinction. Here we trained animals to self-administer cocaine and extinguished them in the presence or absence of VNS. VNS-treated animals had increased rates of extinction and showed reductions in cue-induced reinstatement. After reinstatement, we performed in-vivo recordings of evoked local field potential in the basolateral amygdala (BLA) of anesthetized animals to assess VNS-induced changes in plasticity in the pathway between the medial prefrontal cortex (PFC) and the BLA. Stimulation of the infralimbic PFC (900 pulses at 1Hz) induced LTD in Sham-VNS animals, but caused no change in VNS animals. The data suggest that VNS facilitates extinction and reduces reinstatement by modulating the projection from the PFC to the BLA. These findings provide systems-level information about neural plasticity during extinction and suggest a novel approach for the treatment of drug addiction.

Colon LM, Santarelli A, Odynocki N, Poulos AM *U Albany*

Retention of long-term context fear memories across development in female and male Long Evans rats Evidence suggests that biological sex and developmental age are two factors known to impact an individualâĂŹs vulnerability or resilience to developing anxiety disorders, including PTSD (Salmon & Bryant, 2002). To date, relatively little available evidence that animal models of fear-related PTSD symptoms, such as Pavlovian fear conditioning exhibit interactions between developmental age and biological sex. The present study examined fear acquisition and retention across multiple stages of development. Both male and female Long Evans rats across four developmental periods were tested: pre-adolescence (P24), early adolescence (P33), late adolescence (P37) and early adulthood (P60). Rats were initially trained with three tone- shock parings and context fear and generalization were tested in both the original training context and a novel context at either recent (1d) or remote (14d) retention intervals. Our results indicate that developmental age and sex are key variables that regulate the retention and specificity of fear memories.

Crystal JD *Indiana U*

Animal models of episodic memory Representations of unique events from one's past constitute the content of episodic memories. The central hypothesis about an animal model of episodic memory is that, at the moment of a memory assessment, the animal retrieves a memory of a specific earlier event. I will describe a number of approaches toward developing animal models of episodic memory using rats. A range of approaches were used to model elements of episodic memory. The approaches include: what-where-when memory (Zhou & Crystal, 2009, PNAS), source memory (Crystal, Alford, Zhou & Hohmann, 2013, Current Biology), binding of episodic memories (Crystal & Smith, 2014, Current Biology), memory of a stream of multiple items in context (Panoz-Brown, Corbin, Dalecki, Gentry, Brotheridge, Sluka, Wu & Crystal, in press, Current Biology), and answering an unexpected question after incidental encoding (Zhou, Hohmann & Crystal, 2012, Current Biology). Although any single approach is characterized by a pattern of strengths and weaknesses, the diversity of approaches may promote the development of converging lines of evidence on the problem of assessing episodic memory in animals. *R01MH080052, R01MH098985, R21AG051753*

Czarnecki LA, Moberly AH, Fast CD, & McGann JP *Rutgers*

Violating learned expectations shapes sensory input to the brain Mammals learn contingencies among stimuli in their sensory environment, thus establishing expectations that can influence neural processing of sensory stimuli. Here we show that establishing and violating expectations about the presentation of a tone cue can influence sensory processing of odors as early as the first synapse in the olfactory system. We performed wide-field in vivo imaging from awake, head-fixed OMP-synaptopHluorin mice. In these mice, expectations were established by repeatedly presenting 13 light-tone-odor sequences and then violated by omitting the expected tone while presenting the light and odor as usual. There was a suppression of odorant-evoked neurotransmitter release from OSNs during the surprising odorant presentation compared to the previous expected, tone-cued odorant presentation. This effect was not observed if mice were anesthetized or if the absence of the tone was unsurprising. Pupillometry revealed dilation of the mouseâĂŹs pupil that began shortly after odor onset and was absent on the preceding three tone-present trials. Imaging of sniff-by-sniff calcium dynamics in OSN presynaptic terminals revealed that suppression of activity is present on the first inhalation of odorant during the surprising trial. This suggests a GABAB receptor-mediated presynaptic inhibition, so we repeated the experiment in GAD2-GCaMP3 mice where we could visualize the activity of GAD65-expressing periglomerular interneurons. Consistent with this hypothesis, we observed an increase in GCaMP signals during the first inhalation of odorant on the surprising trial. We then systemically blocked GABAB receptors with CGP35348 and observed removal of a tonic presynaptic inhibition of OSN terminals, after which the surprising omission of an expected tone no longer had any effect

on odorant-evoked neurotransmitter release. To test whether non-olfactory stimuli themselves convey predictive information to the olfactory system, mice were again presented with 13 trials of the light-tone-odor sequence, but on the 14th trial, the odor was omitted and the response evoked by the odor-predictive stimuli was observed. On this odor-omitted trial, the magnitude of GCaMP signals was not significantly different from the previous odor-present trial. These experiments suggest that expectations and surprise can shape sensory processing as early as the primary input into the brain. *NIH grants DC009442 and DC013090 to JPM*

Daw ND *Princeton*

A computational view on actions and habits. In part because of the computational complexity of exactly computing utilities in expectation over a series of future states, it is believed that human and animal brains use a range of shortcuts to simplify or approximate evaluation in sequential tasks such as mazes or chess. In particular, pre-computing (via model-free reinforcement learning) and storing action preferences has been taken as a formal model of habits – both healthy and in disorders such as drug abuse – and fuller, model-based evaluation is a candidate computational theory for goal-directed action. I review evidence that humans and animals trade off deliberative and habitual strategies to action evaluation, and then turn to in-progress research investigating additional possibilities outside this dichotomy. These hybrid theories enrich the notions of habit and deliberation, and also further complicate attempts to build a resource-rational account of the arbitration between actions and habits.

De Corte BJ, Matell MS, & Narayanan NS *U Iowa*

Investigating how input to and output from the striatum mediates interval timing We evaluated how input to and output from the striatum mediates interval timing, the perception of time in the seconds to minutes range. First, we tested whether frontal input to the striatum mediates interval timing performance. Rats were trained on a discrete-trial, fixed-interval schedule in which a houselight was presented and reward is delivered for the first response that occurred after a specified duration (12 seconds) elapsed. While rats performed the task, we recorded from either the medial frontal cortex (MFC) or the dorsomedial striatum (DMS). We found a subset of neurons whose activity increased or decreased monotonically throughout the interval (i.e., âĂŸrampingâĂŹ neurons). Then, we trained a flat-prior, naÃŕve Bayes classifier to predict elapsed time within a trial based on the population activity in each area at a given point in time. Classification performance was high in both areas, and dropped when ramping neurons were excluded from the analysis. Critically, when we inactivated the MFC with muscimol, ramping activity decreased; classification performance based on striatal activity dropped considerably; and temporally controlled behavior was impaired. These findings suggest MFC input to the striatum mediates interval timing behavior. Next, we investigated how striatal output via D1 and D2-expressing MSNsâĂŤwhich are thought to control the direct and indirect pathways, respectivelyâĂŤmediates interval timing performance. Rats were trained on a peak interval procedure. Similar to the fixed interval task, during rewarded trials, a houselight was presented, and after a specified duration (6 seconds) elapsed, the first response that occurred resulted in reinforcement delivery. However, probe trials were also included (50% of trials), in which the reward was omitted and the houselight remained on for 18-24 seconds. This allowed us to evaluate how rats decided to start and stop responding based on temporal information. Importantly, prior to starting the task during testing days, we infused rats with saline, a D1 antagonist (SCH-23990), or a D2 receptor antagonist (sulpride) in the DMS. Relative to saline trials, D1 and D2 receptor blockade resulted in a rightward shift in both start and stop times. This contrasts with prior work showing a functional dissociation between D1 and D2 expressing MSNs during non-temporal decision-making tasks.

de Solis CA, Ho A, Holehonnur R, & Ploski JE *UT Dallas*

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

DeAngeli NE, Jiang MY, Bucci DJ, & Todd TP *Dartmouth*

Intact renewal after extinction of conditioned suppression with lesions of either the retrosplenial cortex or dorsal hip-

pocampus. Extinction of fear to a Pavlovian conditioned stimulus (CS) is known to be context-specific. When the CS is tested outside the context of extinction, fear returns, or renews. Several studies have demonstrated that renewal depends upon the hippocampus, consistent with the notion that the hippocampus encodes and retrieves context representations. However, there are also several reports that renewal is not impacted by hippocampal damage, suggesting that under some conditions context encoding and/or retrieval of extinction depends upon other regions. One candidate is the retrosplenial cortex (RSC), which is known to contribute to contextual and spatial learning and memory. Using a conditioned-suppression paradigm, Experiment 1 tested the impact of pretraining RSC lesions on renewal of extinguished fear. Consistent with previous studies, lesions of the RSC did not impact acquisition or extinction of conditioned fear. Further, there was no evidence that RSC lesions impaired renewal, indicating that contextual encoding and/or retrieval of extinction does not depend upon the RSC. In Experiment 2, post-extinction lesions of either the RSC or the dorsal hippocampus (DH) likewise had no impact on renewal. However, RSC and DH lesions did impair performance in an object-in-place procedure. RSC contributions to context and spatial learning and memory are discussed.

Della Valle RB, & Matell, MS *U Delaware*

Spontaneously hypertensive rats show differences in temporal perception and task acquisition in a peak interval procedure Individuals with attention deficit and hyperactivity disorder (ADHD) demonstrate deficiencies in making accurate reproductions of time durations, but no well-supported mechanism for these deficits is currently known. ADHD patients consistently under-reproduce durations, exhibit higher intraindividual variability, and their accuracy decreases with longer durations at a steeper rate than in neurotypical controls. It is currently unknown whether differences in timing behavior in subjects with ADHD are the result of impulsive responding or a deficit in temporal perception. Spontaneously Hypertensive Rats (SHR), a rodent model of ADHD, have not consistently shown the same timing behavior as human subjects in timing tasks. However, animal models are given much more extensive training than human subjects. The current study used a peak interval procedure with 2 cues to demonstrate differences in timing behavior during the early phases of learning the peak interval procedure. SHRs responded significantly earlier than control animals on a 5 second peak interval schedule, but later than controls on a 20 second schedule. Effect sizes were greater in earlier training blocks, suggesting that timing differences in this strain are present early in operant training, but may become nonsignificant with extensive training.

Do Carmo-Blanco N & Jozefowiez J *Charles de Gaulle Lille*

Attentional load might explain the superiority of spaced over massed trial spacing in human contingency learning While it is well-known that associative learning proceeds faster when trials are spaced rather than massed, the explanation of this classic result has remained somehow elusive. In the present series of experiment, we combined a dual-task paradigm with a streamed-trial contingency assessment procedure in order to bring light to this phenomenon. Participants watched rapid flows of visual stimuli at the end of which they had to assess whether an outcome was contingent upon a cue, which was the case in half of the stimulus flows. The inter-trial interval (ITI) was either 100 ms or 1000 ms and the participants performed the task either by itself (control condition) or performed a concurrent task at the same time ranging from one with a low attentional demand (articulatory suppression) to one with a very high attentional demand (counting backward three by three). In the control condition, we observed the classic spaced versus massed trial effect: The participants were better at discriminating between the contingent and non-contingent flows when the ITI was 1000 ms. The concurrent task had a small impact on the contingency discriminability in the 100-ms flows but that effect did not scale with cognitive load. On the other hand, in the 1000-ms flows, performance decreased as the cognitive load of the dual task increased, to the point that the difference with the 100-ms flows slowly vanished. Our interpretation of these results is that, during the 1000-ms ITI, the participants engage in some kind of cognitive activities which allowed them to better the cue-outcome contingency. The need for the constant visual buffering of the stimuli in the 100-ms would not allow the participants to engage in that activity hence explaining the better contingency discrimination in the 1000-ms condition. The nature of that cognitive activity will be the target of future studies but two things can already be said about it. First, it requires attentional ressource as it is suppressed by a cognitively demanding dual task. Second, as all the dual tasks we used equally taxed the phonological component of working memory, it is not verbal in nature.

Doyère V *Paris-Saclay Institute of Neuroscience (Neuro-PSI)*

Timing the CS-US interval: A role for the Amygdala? In Pavlovian aversive conditioning, the subject not only learns an association between a neutral conditioned stimulus (CS) and an aversive unconditioned stimulus (US), but also that the CS predicts the time of arrival of the US. I present a series of experiments combining immunohistochemistry, local pharmacology and in vivo local field potential recordings in awake rats during auditory fear/threat conditioning. Results showed that the basolateral amygdala participates in the processing of temporal expectancy for the US arrival, and regulates both plasticity mechanisms in the dorsomedial striatum and flexible adaptation to changes in the CS-US interval. As a whole, the results suggest that the dorsomedial striatum and basolateral amygdala belong to a common func-

tional network underlying temporal expectancy in Pavlovian conditioning. *CNRS LIA LearnEmoTime; Partner University Fund; National Research Agency (ANR)*

Driskill C, Duzdabian H, Phensy AJ, & Kroener S *UT Dallas*

N-acetyl cysteine treatment prevents behavioral deficits in an NMDA receptor dysfunction model of schizophrenia Glutamate hypotheses of schizophrenia are based on the observation that NMDAR antagonists like ketamine or phencyclidine induce positive, negative, and cognitive symptoms of the disease in healthy subjects, or exacerbate the symptoms in patients. We have previously shown that treatment with ketamine during the second postnatal week produces long lasting behavioral deficits in mice that are similar to the cognitive and negative symptoms found in schizophrenia (Jeevakumar et al. Behav. Brain Res. 2015). Oxidative stress has been implicated as an important factor in the etiology of schizophrenia. Here we tested whether N-Acetyl-Cysteine (NAC), a precursor to the antioxidant glutathione, can prevent the emergence of ketamine-induced behavioral deficits. Therefore we used a battery of tests that model positive, negative, and cognitive symptoms of schizophrenia in rodents. NAC prevented ketamine-induced deficits in an attentional set shifting task, a novel object recognition task, a spontaneous alternation task, and social recognition task. These results show that prophylactic treatment with NAC can prevent the emergence of schizophrenia-like symptoms in a developmental NMDA dysfunction model of the disease.

Dutta S, Gilman TL, Cecil C, Adkins JM, & Jasnow AM *Kent State*

Thy1 Neuron Activation in the BLA Promotes Fear Inhibition and Reduces Defeat-Induced Social Inhibition Thy1 neurons are a subset of glutamatergic neurons found throughout the brain, including in the basolateral amygdala (BLA). Previously we have demonstrated that optogenetic activation of BLA Thy1 neurons attenuates cued fear learning and enhances cued extinction learning, suggesting that BLA Thy1 neuron activity promotes inhibition of fear. To further investigate these findings, we employed designer receptors exclusively activated by designer drugs (DREADDs) to selectively activate BLA Thy1 neurons. Adult male Thy1-Cre mice were stereotaxically infused with a Cre-dependent virus coding for the activational (Gs) DREADD rM3D. This permitted selective activation of only BLA Thy1 neurons during either a passive avoidance paradigm to investigate contextual fear processing, or a social defeat paradigm to examine defeat-induced social withdrawal. For passive avoidance, BLA Thy1 neurons were activated at one of three time points: after initial training, after extinction training, or before testing. With respect to social defeat stress, BLA Thy1 neurons were activated either after each of the two defeat sessions, or before social interaction testing. We found that activating BLA Thy1 neurons after initial and extinction trainings resulted in decreased expression of fear 48 h later, whereas there was no effect when these neurons were activated 30 min before testing. Further, BLA Thy1 neuron activation was effective in reducing fear following a 10 min extinction training session, but not after a 5 min session, suggesting that a threshold of learning must be satisfied in order for these neurons to successfully promote fear inhibition. In contrast, activating BLA Thy1 neurons after social defeat stress (24 and 48 h before social testing) did not affect social interaction. However, activating these neurons 30 min prior to testing increased social investigation selectively in defeated animals, without influencing social interaction of non-defeated control mice. Overall, these findings indicate that BLA Thy1 neurons inhibit fear behavior and defeat-induced social avoidance through temporally distinct mechanisms. Future work will be directed at dissecting the downstream brain regions responsible for the immediate effects of BLA Thy1 neuron activation on reducing social inhibition and the longer-term influence on fear and extinction learning. *Whitehall grant*

Eddy MC, Todd TP, DeAngeli NE, Huszár R, & Bucci DJ *Dartmouth*

Retrosplenial cortex lesions produce retrograde and anterograde context amnesia following overtraining The retrosplenial cortex (RSC) is positioned at the interface of primary cortical sensory areas and the parahippocampal-hippocampal memory system and is thus well suited to contribute to learning and memory processes. Indeed, the RSC has been shown to have an important role in both spatial and contextual learning. For example, both pre- and post-training lesions of RSC attenuate contextual fear conditioning. Still, the system or pathways that support contextual fear conditioning appear to be dynamic (Fanselow, 2010). For example, pre-training lesions of the hippocampus produce deficits with weak training (e.g., 1 shock). However, with overtraining (e.g., more than 3 shocks) pre-training hippocampus lesions do not affect contextual fear conditioning. Thus, with enough training, the hippocampus is not required for context learning. The purpose of the current experiment was to examine the role of the RSC in contextual fear conditioning after overtraining. Rats underwent training where they received 25 tone-shock pairings in Context A. The next day, rats received either sham or RSC lesions. Following 14 days of recovery, all rats were tested for context memory in Context A. We found that RSC-lesioned rats exhibited less freezing behavior than sham-lesioned controls. A subsequent test of tone-specific fear in Context B revealed no differences between groups, indicating that RSC lesions produced a selective deficit in contextual fear. All rats were then trained in Context B with 25 tone-shock pairings. Fourteen days later, context memory was tested in Context B and tone fear tested in Context C. RSC-lesioned rats once again exhibited attenuated freezing behavior, while there were no differences between groups in

tone fear. Overall, lesions of the RSC produced both retrograde and anterograde deficits with overtraining in a contextual fear conditioning paradigm. In contrast, previous studies have demonstrated that hippocampal lesions produce retrograde, but not anterograde, amnesia following overtraining (e.g., Wiltgen, 2006). Thus, the current studies suggest that RSC has essential role in contextual fear conditioning and that other systems or pathways are unable to compensate for the loss of RSC function.

Ely SL & Wilson WJ *Albion*

The Effects of MK-801 on Escape Behavior in the Earthworm, Lumbricus terrestris We have previously shown that earthworms (Lumbricus terrestris) can engage in escape behavior, increasing locomotion to turn off an aversive light stimulus. The NMDA antagonist MK-801 blocks this learning completely at a dose of 0.1 mg/ml (administered cutaneously). We extended our examination of MK-801's effect to lower doses. Each Master-Yoked pair of earthworms (64 pairs total) was given saline or one of three doses of MK-801 (0.01, 0.05, and 0.1 mg/ml, administered by wrapping the worm in plastic wrap with the drug for 2 min). Escape behavior was assessed in computerized running wheels; after a 20-min acclimation period in darkness, a bright LED turned on and remained on for a 4-hr period unless the worm moved. Movement in the light turned off the light for 1 min; in the dark movement reset the time until light returned to 1 min. MK-801 reduced escape behavior in a dose-dependent manner, suggesting that NMDA-like receptors play a role in learning in earthworms as they are known to do in vertebrate species. *Albion College Foundation for Undergraduate Research, Scholarship, and Creative Activity*

Farley SJ & Freeman JH *U Iowa*

Reversible Inactivation of Amygdala Central Nucleus Impairs Delay Eyeblink Conditioning with a Visual Conditioned Stimulus Amygdala modulation of cerebellar-mediated conditioned responses (Siegel et al, 2015) and deep cerebellar nuclei plasticity (Farley et al, 2016,) have recently been demonstrated. A candidate mechanism is that amygdala output may modulate the conditioned stimulus (CS) pathway in eyeblink conditioning (EBC). However, it is unknown if the amygdala modulation is specific to EBC with an auditory CS. To address this, we trained adults rats in delay EBC as previously reported (Farley et al, 2016), but used a white LED as the CS. Adults rats were bilaterally implanted with cannulae directed at the amygdala central nucleus (CeA). Rats were divided into three groups: MUS (muscimol [GABA-A agonist]), SAL (saline), MUS-EXT (extensive training with muscimol). The MUS and SAL groups received muscimol (2mM, 0.2Îijl) or saline infusions 30 minutes prior to training during sessions 1-5. Training continued without infusions from session 6 to reaching criterion. Saline and muscimol retention tests were then given to all rats (order counter balanced). The CS was switched to an auditory CS and rats reacquired delay EBC. After reaching criterion, rats were given retention tests again with saline and muscimol infusions. For the MUS-EXT group, rats were trained for 16-sessions with CeA inactivation. Training continued without inactivation from session 17 until reaching criterion, after which they underwent a muscimol retention session. Acquisition of delay EBC with a visual CS was severely impaired with CeA inactivation during the first 5 sessions. Rats in the MUS-EXT group showed a modest increase in CRs by the end of training. There were no differences in the rate or magnitude of other eyeblink measures (unconditioned responses, startle responses, etc) during the initial LED training. The number of sessions to reach criterion without inactivation was the same between muscimol and saline animals across CS modalities. After rats in the MUS-EXT group reached criterion, their CRs were impaired with a muscimol retention session and then CRs recovered to pre-retention levels the following session. These results show that CeA inactivation impairs the acquisition and retention of delay EBC with either a visual or auditory CS. Furthermore, despite some learning of the CS-US association during extensive training with CeA inactivation, amygdala output appears to have a persistent role in the acquisition and retention of delay EBC. These results are consistent with previous findings that amygdala output to the pontine nucleus may strongly modulate CS information to the cerebellum. *NS088567*

Foilb AR, Flyer-Adams JG, Maier SF, & Christianson JP *Boston College*

Posterior insular cortex is necessary for conditioned inhibition of fear, but not fear discrimination. Discriminating between danger and safety is critical to survival. Learned safety signals inhibit fear responses evoked by contemporaneous danger signals, a phenomenon termed conditioned inhibition of fear. Here, rats received CS+/CS- fear discrimination conditioning over 5 days and received a summation test 24 hours later in which freezing, an index of fear, was assessed during exposure to the context alone, CS+, CS+ and CS- in compound (summation) and CS- alone. Injections of NMDA-receptor antagonist AP5 to posterior insular cortex (IC) before conditioning completely prevented the acquisition of conditioned inhibition of fear, while intra-AP5 to anterior or medial IC had no effect. To determine if the IC contributes to the recall of conditioned inhibition of fear, rats underwent several conditioning sessions, and then injections of GABAA agonist muscimol were made to inactivate the posterior IC before a summation test. This resulted in an overall reduction of fear. Additional experiments sought to determine if the role of the IC in conditioned inhibition learning could be reduced to the simpler function of fear discrimination, which forms after a single conditioning session, but fear discrimination and recall were unaffected by AP5 or muscimol, respectively, in the posterior IC. These data sug-

gest that posterior IC is necessary for conditioned inhibition, but not fear discrimination. *NIH Grant MH093412 and the Brain and Behavior Research Foundation to J.P.C.*

Fontanini A *Stony Brook*
Anticipatory activity in the gustatory cortex of alert rodents Sensory cortices are typically studied for their ability to encode unisensory stimuli. The gustatory cortex (GC) is no exception, as it has been mostly investigated for its role in processing taste. However, recent evidence shows that GC can be activated by taste-predictive stimuli of various sensory modalities. In this presentation, I will discuss data from my laboratory showing how neurons in GC can encode expectations. First, I will discuss results from multielectrode recordings in GC of rats engaged in a general expectation paradigm. These data will be used to support the conclusion that GC can encode the general expectation of gustatory stimulation, a phenomenon that affects sensory coding. Then, evidence from a study in rats performing an auditory go/no-go task will be presented. These results will be used to demonstrate that GC can represent specific expectations and that this ability depends on learning. Finally, I will present data from a study showing how stimuli of all four sensory modalities (olfaction, somatosensation, audition and vision) are represented in GC of rats before and after associative learning. Altogether, these studies will provide a comprehensive view of how learning can endow the primary gustatory cortex with the ability to predict future stimuli. *NIDCD*

Freeman JH, & Farley SJ *U Iowa*
Amygdala Modulation of Cerebellar Learning Memory for the emotional significance of stimuli provides essential contextual information for acquisition and expression of motor responses. We conducted a series of studies to examine the role of the amygdala in cerebellum-dependent eyeblink conditioning in rats to elucidate the mechanisms underlying amygdala-cerebellum interactions. Inactivation of the central amygdala (CeA) severely impairs acquisition and retention of eyeblink conditioning, indicating that the amygdala continues to interact with the cerebellum after conditioning is consolidated. CeA inactivation also substantially reduces stimulus-evoked and learning-related neuronal activity in the cerebellum during eyeblink conditioning. Monosynaptic projections from the medial CeA to the pontine nucleus and medial auditory thalamus may support amygdala modulation of auditory CS input to the cerebellum. Further evidence that the CeA modulates cerebellar learning through the CS pathway comes from an experiment that used middle cerebellar peduncle (mcp) stimulation as the CS to bypass the pre-cerebellar CS pathway. CeA inactivation had no effect on acquisition of eyeblink conditioning with mcp stimulation as the CS, indicating that CeA modulation occurs through the CS pathway. Previous theories of amygdala-cerebellum interactions posited that the amygdala forms a fear-based memory that then facilitates acquisition of a motor memory in the cerebellum. We found that manipulations that impair consolidation of fear conditioning have not effect on eyeblink conditioning, suggesting that the modulation mechanism does not require LTM formation. The findings suggest a model of amygdala-cerebellum interactions in which the amygdala gates conditioned stimulus inputs to the cerebellum within training sessions. Amygdala gating of sensory input to the cerebellum may be an attention-like mechanism that facilitates cerebellar learning. *NS-088567*

Freestone DM, & Myers KP *Bucknell*
The effects of habitual sugar consumption on interval timing in rats. Drugs that modulate dopamine impact interval timing. Habitual sugar consumption is an experiential manipulation of dopamine. In the short term, sugar intake stimulates dopamine release, but the effects of habitual consumption are much more complex. Thus, effects of habitual consumption on timing might be seen on precision, accuracy, or some other aspect of timed behavior. We ran 24 rats on the Switch task in which both timing precision and accuracy could be precisely measured. Male and female rats were randomly assigned to a habitual sugar consumption condition or control. Rats in the sugar condition were given ad lib access to sugar for a month before starting behavioral testing, and then 20 ml each day during testing. All rats were maintained at 85% of their free feeding weight. Rats were trained on a switch task in which intermixed trials of either a short (3 s) or long (9 s) duration were signaled by the same stimulus. Rats were reinforced on "Short" trials for the first press on the "Short" lever after 3 s elapsed, and during "Long" trials for first press on the "Long" lever after 9 s. Rats begin by holding down the "short" lever and then switch to the "long" lever, if some amount of time has elapsed without a reinforcer. This switch time is a real-time behavioral measure of their criterion for classifying the duration as short or long, and its distribution over trials gives a measure of timing accuracy and precision. Preliminary analysis of behavior during acquisition suggests that habitual sugar consumption may lead to an initial decrease in precision but may not change accuracy. To our knowledge, this is the first evidence of the potential effect of dietary habits on interval timing.

Gallegos M, & Sánchez-Carrasco L *UNAM*
Inhibitory associations Context-Response delay the reacquisition of instrumental responding on ABA renewal design. Bouton & Todd (2014), as well as Todd (2013), have suggested that instrumental extinction results in a direct inhibitory association between the context and the response. To further test this prediction, in this experiment, we assessed the reacquisition of lever pressing using ABA, ABC, and ABB renewal designs. During the acquisition phase, lever pressing was reinforced in Context A for seven sessions in all groups. Then lever pressing was extinguished in Context B, during six sessions. Finally, in the test phase reinforcement was reintroduced and subjects in ABA group were re-

trained in Context A, subjects in ABC group in context C and subjects in ABB group in Context B. Results showed a slower reacquisition when the extinction context was present. *DGAPA-PAPIIT 305815*

Giustino TF, Seemann JR, Acca GM, & Goode TD, Fitzgerald PJ, & Maren S *Texas A&M*
Beta noradrenergic blockade in the basolateral amygdala, but not the medial prefrontal cortex, rescues the immediate extinction deficit Early intervention strategies such as psychological debriefing and exposure therapy are widely practiced following a traumatic experience. These therapies are aimed at reducing the development of stress and trauma-related disorders (e.g., anxiety, phobias, and post-traumatic stress disorder) and are thought to rely on extinction like-processes. However, animal models and human research suggest extinction training often fails to reduce fear long term when administered soon (minutes to hours) after trauma. This is likely due to high levels of psychological stress in the wake of trauma, yielding an immediate extinction deficit (IED). We have previously shown that systemic beta-adrenoceptor blockade (propranolol, 10 mg/kg, i.p.) delivered immediately after fear conditioning (and 30 min prior to immediate extinction training) rescues the IED. In contrast, propranolol administered 30 min prior to delayed extinction (24 hrs post conditioning) produced retrieval deficits. The neural substrates underlying these effects remain largely unknown. Here animals underwent a standard auditory fear conditioning procedure and then received either immediate (30 min after conditioning) or delayed (24 hrs after conditioning) extinction training. We used intracranial infusions of propranolol prior to immediate or delayed extinction targeting either the infralimbic (IL) subdivision of the medial prefrontal cortex or the basolateral amygdala (BLA) to examine the effects of beta adrenoceptor blockade on extinction learning. Interestingly, intra-BLA, but not intra-IL, propranolol rescued the IED; that is, animals receiving intra-BLA propranolol prior to immediate extinction showed less spontaneous recovery of fear during extinction retrieval. In contrast, neither intra-BLA nor intra-IL propranolol modulated delayed extinction learning. Overall, these data contribute to a growing literature suggesting dissociable roles for key nodes in the fear extinction circuit depending on the timing of extinction relative to conditioning. These data suggest heightened noradrenergic activity in the BLA underlies extinction deficits during high psychological stress. Propranolol may be a useful adjunct to therapeutic interventions in recently traumatized individuals who are at risk for developing trauma-related disorders. *NIH grant R01MH065961*

Glanzman DL, Pearce K, Cai D, & Chen S *UCLA*
Role of DNA Methylation in the Maintenance of Long-Term Memory in Aplysia Mammalian studies have identified a major role for DNA methylation in the maintenance of long-term memory (LTM). Here, we investigated whether the maintenance of the LTM for behavioral sensitization in Aplysia depends on DNA methylation. Animals were given sensitization training consisting of five spaced bouts of electrical shocks delivered to the tail via implanted electrodes (5X training). This training induces long-term sensitization of the siphon-withdrawal reflex (SWR) that persists for at least a week. At various times, ranging from 24 h to 5 d, after the initial 5X training animals received an intrahemocoelic injection of either RG108, a DNMT inhibitor, or vehicle solution. Inhibition of DNMT disrupted LTM as assessed by a test of the SWR made 24 h after the injection. Recently, we showed that consolidated LTM could be reinstated following its disruption by reconsolidation blockade (Chen et al., 2014) by giving animals truncated sensitization training, comprising three spaced bouts of tail shocks (3X training). Accordingly, we tested whether 3X training could reinstate the LTM disrupted by inhibition of DNMT. Unlike in the case of memory reconsolidation blockade, however, 3X training failed to reinstate LTM; thus, administration of RG108 appeared to abolish fully consolidated LTM. In additional experiments we observed that an injection of a different DNMT inhibitor, 5-azadeoxycytidine (5aza), when made as late as 5 d after 5X training, also abolished LTM. We found that LTM could be reestablished following its elimination by DNMT inhibition if animals were retrained using five bouts of tail shocks (5X training); thus, the amnestic effect of the DNMT inhibitors could not be attributed to adverse effects of the drugs on the animalsâĂŹ health. Because DNA methylation is commonly associated with gene silencing, our results suggest that persistent downregulation of the expression of one or more memory suppressor genes plays an essential role in the maintenance of LTM in Aplysia. *NIH R01 NS029563 and R01 MH096120*

Goode TD, Acca GM, & Maren S *Texas A&M*
Reversible inactivation of the bed nucleus of the stria terminalis disrupts the expression of fear to unpredictable conditioned threats The bed nucleus of the stria terminalis (BNST) is thought to control conditioned fear responses to contexts but not short-duration cues. However, a conditioned context may inevitably differ from a discrete cue in terms of when the animal expects an aversive event to occur during presentation of the stimulus. The current experiments sought to examine whether unconditioned stimulus (US) predictability is a factor in the recruitment of the BNST, independent of conditioned stimulus (CS) duration. First, to establish a strong vs. weak predictor of footshock, rats underwent either forward (i.e., CS-then-US) or backward (i.e., US-then-CS) fear conditioning. Specifically, we hypothesized that the expression of fear to the less predictable (backward) CS would be mediated by the BNST, whereas expression of a forward-trained CS would not. In Experiment 1, rats received twelve forward CS (10 sec, 2 kHz, 80 dB auditory cue)-then-US (2 sec, 1.0 mA footshock) pairings (”FW”) or twelve backward

US-then-CS pairings ("BW") in Context A (60-sec intertrial intervals, ITIs). Freezing served as the dependent measure of fear. The next day, rats underwent 1 hr of context extinction in the conditioning context or equivalent exposure to a novel context (Context B). 24 hrs later, rats were tested to the auditory CS (eight CS-only trials; 60-sec ITIs) in a separate novel context (Context C). Both forward and backward conditioning resulted in robust fear; fear to the BW but not FW CS was susceptible to extinction of the conditioning context. In Exp. 2, naÃŕve rats were implanted with cannulae targeting the BNST. 1 week after surgery, rats were trained to a FW or BW CS as in Exp. 1, with another group receiving 5 FW conditioning trials instead of 12. 24 hrs after conditioning, rats were infused with the AMPA receptor antagonist, NBQX, or vehicle immediately prior to 12 CS-only testing trials (60-sec ITIs) in a novel context. Intra-BNST infusions of NBQX blocked fear expression to the BW CS, but did not significantly alter fear expression to the 5- or 12-training trials FW CS. A third experiment demonstrated that BNST inactivation disrupted fear expression to a previously conditioned context in which shock (2 sec, 1 mA) was experienced long after placement in the chamber (9 min, âĂIJunpredictableâĂİ) compared to a context within which shock was experienced soon after placement (1 min, âĂIJpredictableâĂİ). These results suggest that fear evoked by unpredictable CSs, whether contexts or cues or long- or short-duration stimuli, are mediated by the BNST. *NIH (R01MH065961 to SM, F31MH107113 to TDG)*

Grissom N *U Minnesota*

Male-specific deficits in reward learning in mouse models of autism

Neurodevelopmental disorders, including autism spectrum disorders (ASD), are highly male biased, but the underpinnings of this are unknown. Striatal dysfunction has been strongly implicated in the pathophysiology of neurodevelopmental disorders, raising the question of whether there are sex differences in how the striatum is impacted by genetic risk factors linked to neurodevelopmental disorders. We have identified male-specific deficits in striatal function important to reward learning in a mouse model of 16p11.2 hemideletion, a genetic mutation that is strongly associated with risk of neurodevelopmental disorders, particularly autism and ADHD. We find that male, but not female, 16p11.2 deletion animals show impairments in reward-directed learning and maintaining motivation to work for rewards. Male, but not female, deletion animals overexpress mRNA for dopamine receptor 2 and adenosine receptor 2a in the striatum, markers of medium spiny neurons signaling via the indirect pathway, associated with behavioral inhibition. Despite equivalent effects in males and females on the mRNA levels of genes located within the 16p11.2 region in the striatum, including the kinase ERK1, hemideletion males show increased activation in the striatum for ERK1 at baseline and in response to sucrose, a signaling change associated with decreased striatal plasticity. In contrast, we find that hemideletion females show increased protein for ERK1 as well as the related kinase ERK2, and no change in phosphorylation either at baseline or in response to sucrose. These data indicate male-specific vulnerability in the mechanisms regulating intracellular signaling in the brain as a result of a genetic lesion. Interestingly, our work indicates that other mouse models of autism also show deficits in reward learning, suggesting this as a common behavioral endophenotype of models of autism.

Handy JD, Avcu P, Ko N, Ortiz A, Liberzon I, Marx C, Doria M, & Servatius RJ *Rutgers*

Facilitated Acquisition of the Conditioned Eyeblink Response in Active Duty Military Expressing Type D Personality and BI Temperament Background: Type D (distressed) personality, characterized by high negative affectivity and social inhibition, is a vulnerability factor for PTSD. In previous work, facilitated acquisition of the classically conditioned eyeblink response was demonstrated in civilians expressing behaviorally inhibited (BI) temperament, and veterans with PTSD symptoms. A recently completed study examined whether biases in eyeblink conditioning are apparent in active duty Coast Guard (CG) personnel expressing Type D personality. Method: 79 active duty CG personnel (15 females), aged 18 to 46, were recruited from 5 Boat Stations. PTSD symptoms were assessed using the PTSD checklist (PCL) with military (PCLM) and non-military (PCL-C) prompts (DSM-IV criteria). Type D personality was assessed with the DS14 and BI temperament with the adult measure of behavioral inhibition (AMBI). Delay eyeblink conditioning (500-ms pure tone conditioned stimulus [CS] coterminating with a 100-ms air-puff unconditional stimulus [US]) was assessed under a 50% partial reinforcement training schedule in which half of the acquisition trials were CS-alone trials interpolated with standard CS-US paired trials. Results: Consistent with earlier work, facilitated acquisition of the eyeblink response was apparent in BI temperament. Facilitation was also apparent in Type D personality, predominately related to the social inhibition component. Both personality dimensions were associated with greater PTSD symptoms. Rates of learning did not predict PTSD symptoms. Conclusions: Inhibition and withdrawal are strongly associated with learning biases and PTSD symptoms. As a potential vulnerability, learning biases may be secondary to personality traits of inhibition and withdrawal.

Heroux NA, Buban KN, Robinson-Drummer PA, Rosen JB, & Stanton ME *U Delaware*

Inactivation of the medial prefrontal cortex (mPFC) impairs the retention of a context-shock association in the CPFE but not sCFC The context preexposure facilitation effect (CPFE) is a contextual fear conditioning paradigm in which acquiring a context representation, acquiring the context-shock association, and retrieval of contextual fear are temporally disso-

ciated into three distinct phases. In contrast, learning about the context and the context-shock association happens concurrently in standard contextual fear conditioning (sCFC). Our lab has previously shown that both the CPFE and sCFC induce the expression of the inducible plasticity-associated transcription factor Egr-1 in the medial prefrontal cortex of adolescent and adult rats (Schreiber et al., 2014; Chakraborty et al., 2016). The current set of experiments begins to explore the causal role of the mPFC in both variants of contextual fear conditioning by utilizing intra-mPFC infusions of the GABAA receptor agonist muscimol prior to context-shock learning in sCFC and the CPFE. Acquisition of the context-shock association was behaviorally assessed via postshock (acquisition) and 24-hour (retention) freezing tests. Intra-mPFC infusions of muscimol (0.5 Îijg/0.25 Âţl/side) 15 min prior to context-shock training in the CPFE (24 hours after context preexposure) impaired 24-hr retention test freezing but left post-shock freezing intact. Furthermore, muscimol infusions prior to conditioning in sCFC also did not significantly impair postshock freezing. In contrast to the CPFE, retention test freezing was spared following muscimol infusions in sCFC. Our findings suggest that the mPFC is not necessary for the acquisition of the context-shock association in either sCFC or the CPFE. Additionally, activation of the mPFC during conditioning is necessary for later 24-hr retention performance in the CPFE but not sCFC. Whether this difference reflects a role of the mPFC in consolidation, retrieval or some other mechanism of long-term retention performance remains an avenue for future research. Future experiments will also examine the role of the mPFC in the ontogeny of contextual fear learning within the CPFE across normal and abnormal development. *NIH grant R01 HD075066-01A1 to MES and JBR*

Hesslow G, Jirenhed DA, Johansson F, Rasmussen A *Lund*

Temporal memory in cerebellar Purkinje cells A popular idea, usually associated with Cajal and Hebb, is that learning in the nervous system consists in strengthening or weakening of synaptic transmission. A problem with this approach is that it cannot easily account for timing of neural responses. An example is Pavlovian eyeblink conditioning. Repeated pairings of a tone and an air puff to the eye causes acquisition of a conditioned blink that is adaptively timed. This learning takes place in the cerebellum where adaptively timed pauses in spontaneous Purkinje cell firing drive the overt behaviour. The learning mechanism usually invoked to account for the pauses has been long-term depression of parallel fibre to Purkinje cell synapses. The timing was thought to depend on temporal code in the input signals to the cell, due to various delays. Depression of synapses that are active at the right time would then results in appropriately timed responses. Results from our lab have shown that timing of Purkinje cell response does not depend on a temporal code in the input signal and suggest instead that the timing information is stored within the Purkinje cell by a novel learning mechanism. This is also supported by findings that the pauses are elicited by metabotropic glutamate receptors. This forces a revision of our view of learning in the cerebellum and also of the traditional Cajal-Hebb paradigm.

Holland P *Johns Hopkins*

Effects of amygdala lesions on overexpectation phenomena in food cup approach and autoshaping procedures Prediction error (PE) plays a critical role in most modern theories of associative learning, by determining the effectiveness of conditioned or unconditioned stimuli (CS or USs). Here, we examined the effects of lesions of central (CeA) or basolateral (BLA) amygdala on performance in overexpectation tasks. In two experiments, after two CSs were separately paired with the US, they were combined and followed by the same US. In a subsequent test, we observed losses in strength of both CSs, as expected if the negative PE generated on reinforced compound trials encouraged inhibitory learning. CeA lesions, known to interfere with PE-induced enhancements in CS effectiveness, reduced those losses, suggesting that normally the negative PE also enhances cue associability in this task. BLA lesions had no effect. When a novel cue accompanied the reinforced compound, it acquired net conditioned inhibition, despite its consistent pairings with the US, consonant with US effectiveness models. That acquisition was unaffected by either CeA or BLA lesions, suggesting different rules for assignment of credit of changes in cue strength and cue associability. Finally, we examined a puzzling autoshaping phenomenon previously attributed to overexpectation effects. When a previously-food-paired auditory cue was combined with the insertion of a lever and paired with the same food US, the auditory cue not only failed to block conditioning to the lever, but also lost strength, as in an overexpectation experiment. This effect was abolished by BLA lesions but unaffected by CeA lesions, suggesting it was unrelated to other overexpectation effects. *Grant MH53667 from NIH*

Honey R *Cardiff*

Learning about stimuli that are present and those that are not: Dissociating direct and mediated learning Pavlovian conditioning provides a powerful way to probe the nature of associative learning about real-world relationships involving more-or-less prosaic patterns of stimulation. Here, we contrast such instances of direct learning with mediated learning, where an association forms between two memories that is not the product of contiguity between their real-world counterparts. We provide converging evidence, from various sensory preconditioning procedures, that these two forms of learning are dissociable: by variations in the form of the conditioned response, in their differential reliance on a brain systems and neuronal processes, and by the distinct influences of a simple procedural variable. *BBSRC*

Huckleberry KA, Copeland T, Shue F, Yin W, Chitwood RA, & Drew MR *U Texas*
Optogenetic dissection of the contribution of dorsal and ventral adult-born neurons to context fear conditioning The hippocampus contains one of the few neurogenic niches within the adult brain—the subgranular zone of the dentate gyrus (DG)—and exhibits significant functional heterogeneity along its dorsoventral axis. Although adult-born neurons within the DG have been implicated in many hippocampus-dependent behaviors, little is known about how the function of the adult-born neurons varies along this axis. We used a highly specific Nestin-CreER(T2) mouse line (Lagace et al., 2007; Sun et al., 2014) to induce expression of the light-activated neural silencer archaerhodopsin in ≈30% of neural progenitor cells and their progeny. Optical fibers were implanted into the dorsal or ventral DG to selectively silence adult-born neurons in these regions. We first tested the contribution of ⩽6-week-old dorsal and ventral adult-born dentate granule cells to acquisition of context fear memory by delivering laser illumination during training. Silencing neither the dorsal nor ventral adult-born neurons affected the activity burst during the shock, indicating that silencing did not alter shock sensitivity. Context memory expression was tested twenty-four hours after acquisition without laser illumination. While silencing the dorsal adult-born neurons significantly decreased freezing during the context test, silencing the ventral adult-born neurons did not significantly affect freezing during the context test. We next tested the contribution of ⩽6-week-old dorsal adult-born granule cells to context memory retrieval and context generalization. Mice were trained without laser illumination but were tested with laser illumination first in an alternate similar context and next in the original training context (Huckleberry et al., under review). Silencing the dorsal adult-born neurons significantly decreased freezing during testing. Experiments are underway to assess how silencing the ventral adult-born neurons during testing affects context recall and discrimination. In summary, silencing dorsal adult-born neurons during either training and testing reduced context fear memory. Conversely, silencing the ventral adult-born neurons during training did not significantly affect context fear. Additional experiments are also in progress assessing how silencing both dorsal and ventral adult-born neurons alters local neural activity. These data suggest that dorsal and ventral hippocampal adult-born neurons make distinct contributions to memory.

Hui MH, Zelikowsky M, & Anderson DJ *CalTech*
Chronic stress alters fear behavior in a neuromodulator-dependent manner Stress is a powerful experience that effects virtually all animal species. We tested the effects of delivering various forms of stress on subsequent fear behavior using an overhead looming stimulus assay as our behavioral readout. Interestingly, we found that various forms of chronic stress produce an increase in persistent fear responding to the looming stimulus, and that this effect is dependent on the type of chronic stressor employed. Given previous results in the laboratory indicating a role for various neuromodulators in the looming assay, we were interested in exploring the possibility of a larger role for neuromodulators in mediating chronic stress. Combining cre-mouse lines crossed to a fluorescent reporter mouse and applying CLARITY to map brain-wide neuromodulator expression, we found that chronic stress produces an increase in expression of various neuromodulators across brain regions known to encode stress and that this increase correlates with the degree of fear persistence produced by each chronic stressor. Consistent with these data, we found that various perturbations of these neuromodulatory systems in stressed mice was able to block this fear persistence, and that conversely, driving this system in unstressed mice was sufficient to induce persistent fear responding. Collectively, our data point to a broad role for neuromodulators in the regulation of chronic stress. *NSF Postdoc Fellowship 1306215, Samuel N. Vodopia and Carol J. Hasson SURF Fellowship*

Johnson BJ, & Wilson WJ *Albion*
Cross-Species Comparison of Response to Light in Earthworms We compare the responses of the worm Eisenia hortensis and the worm Lumbricus terrestris to bright lights of varying duration. Given their different typical environments, we thought that we might see differences: E. hortensis lives in loose leaf litter, an environment that is subject to disturbance by weather and larger animals, resulting in an increased likelihood of sudden changes in light level. In addition, because E. hortensis are mobile, there is a low cost in moving and responding to a stimuli. L. terrestris's deep burrows are less subject to disturbance, and responses to light that go beyond a simple retreat into the burrow might mean leaving the safety of that permanent home; responding to a stimulus with movement would have a fairly high cost. We placed worms on Duplo boards illuminated by red light for 1 hr, then turned on bright white LEDs for 1, 2, 4, or 8 min for different groups of worms (n= 24 per group). Photos were taken at 10 sec intervals throughout the session. Movement was scored visually by counting the number of pegs past which the worm moved during the light. Measures were standardized to responses/min, and the responses of individual worms were averaged together. E. hortensis moved a lot to short duration lights, and reduced their movement as the light duration increased. In addition E hortensis moved similar amounts during the first minute of each light conditions, with differences in movement for each light condition only arising in the subsequent minutes of the light. L. terrestris had similar movement rates during each light condition, though there were some minor differences between each condition; their response rates to the first minute of light in each condition varied. More species will need to be tested to determine whether this difference is specific to these species, or due

instead to their differing environments. *The Lego Group; Albion Foundation for Undergraduate Research, Scholarship, and Creative Activity*

Kass MD, Rosenthal MC, & McGann JP *Rutgers*
Plasticity of olfactory bulb interneurons after fear conditioning parallels the stimulus specificity of learning Conventional wisdom suggests that the bodyâĂŹs sensory systems should be consistent, so that a given sensory stimulus always produces more-or-less the same signal to the brain, which can then retrieve related memories or information. However, we find that actually these signals are highly flexible, such that previously learned information can radically affect the way sensory stimuli are processed in the brain. Olfactory fear conditioning, for example, can alter the neural representations of odor stimuli as early as the primary sensory input to the brain. This plasticity could be related to learning-induced changes in olfactory bulb glomerular circuitry, which controls sensory input gain through presynaptic regulation of olfactory sensory neuron input and is dynamically regulated by neuromodulatory and cortical networks involved in fear learning. Here, we performed in vivo cell type-specific optical neurophysiology to evaluate the effects of either standard or discriminative olfactory fear conditioning on periglomerular (PG) circuitry in adult mice. Standard fear conditioning consisted of a single day of training with 10 trials of a 15 sec odor (the CS+) paired with a footshock (or 10 shock or odor alone trials for control groups). We compared odor-evoked GCaMP signals in GAD65-expressing PG cells before and after training in each individual mouse, and also measured odor-evoked freezing in a novel context after training. During imaging and test sessions, subjects were presented with a panel of 4 odors including the CS+ and 3 unexposed odors. Fear conditioned mice exhibited stimulus-evoked freezing that generalized across all 4 odors, whereas little freezing was observed in control animals. In parallel, we found that standard fear conditioning resulted in a robust, non-specific enhancement of odor-evoked GCaMP signals in GAD65-expressing PG cells that persisted up to 1 month after training. By contrast, in mice that underwent a discriminative olfactory fear conditioning paradigm (as in Kass, Rosenthal et al 2013) we observed a robust enhancement of odor-evoked GCaMP signals in PG interneurons that was specific to the CS+ and that was correlated with differential cue-evoked freezing. These data show that fear conditioning causes relatively rapid changes in early olfactory coding that are dependent upon the nature of training and are correlated with behavioral outcomes. *This work was supported by the National Institute on Deafness and Other Communication Disorders (R01 DC013090 to JPM and F31 DC013719 to MDK) and the National Institute of Mental Health (R01 MH101293 to JPM) at the National Institutes of Health.*

Keiflin R, & Janak PH *Johns Hopkins*
Phasic Activation of Ventral Tegmental Dopamine Neurons Mimics Reward Prediction Error and Promotes Model-Based Learning Contemporary models of associative learning dissociate between model-free and model-based learning. In model-free learning, animals learn the value of certain cues and actions independently of the representation of their respective outcomes, resulting in rigid behavior insensitive to postconditioning changes in reward value. In contrast, through model-based learning, animals establish an internal model of their environment, connecting certain events with their respective outcome, allowing them to rapidly adjust their behavior following changes in the value of the outcome. Dopamine (DA) neurons in the ventral tegmental area (VTA) have been shown to encode reward prediction error (RPE) and their activation promotes Pavlovian reward learning according to an error-correction principle. However, the relative contribution of this dopaminergic RPE teaching signal to model-free or model-based learning remains unknown. To gain control of VTA-DA neurons and thereby investigate their role in Pavlovian reward learning, we injected TH::Cre transgenic rats with a cre-dependent viral vector coding for channelrhodopsin 2 and implanted optical fibers aimed at the VTA. The rats were then subjected to a blocking paradigm in which learning about a target cue paired with reward is prevented (or blocked) if this cue is presented simultaneously with another cue that already reliably signals reward. In this situation, the absence of RPE, presumably materialized by the absence of phasic DA response, is thought to prevent learning about the redundant target cue. Consistent with the idea that DA neurons encode a RPE teaching signal, we show that optical stimulation of VTA-DA neurons timed with the expected reward mimics a positive RPE and promotes (or unblocks) learning about the redundant target cue. To probe the content of the learning promoted by VTA-DA stimulation, we used the blocking paradigm previously described, combined with postconditioning devaluation of the outcome (via lithium-induced taste aversion). We show that conditioned responding to the target cue was significantly reduced following outcome devaluation, indicating that this response integrated a representation of the outcome. These results contrast with a classic view that assigns DA-RPE to model-free learning and instead provide evidence for a role of phasic VTA DA responses in model-based learning, revealing a complex and unsuspected role of DA in appetitive conditioning.

Kennedy E, Campolattaro MM, & Lipatova O *Christopher Newport*
The Impact of Fornix Lesions on Place Learning in the Open Field Tower Maze Decades of research have provided insight into the underlying behavioral and neural mechanisms that are essential for spatial learning. The hippocampus has been shown to be involved in acquisition of place-, but not response-learning in multiple spatial navigation tasks (e.g., The Morris Water Maze and T-Maze). The present exper-

iment tested whether the hippocampus is necessary for a rat to acquire place-learning in the Open Field Tower Maze (OFTM). The OFTM is a relatively new and non-stressful appetitive task that can be used to examine the underlying mechanisms of spatial learning. After pre-training rats (n = 8) in the OFTM, half of them received fornix lesions and the other half received sham surgeries. We then attempted to train each rat with the place-learning version of the OFTM. Our preliminary results indicate that fornix-lesioned rats require more trails to acquire place-learning relative to sham rats. Therefore, place-learning in the OFTM appears to be hippocampal-dependent. Future experiments will test if the hippocampus is also necessary for response-learning in the OFTM.

Kirry AJ, Herbst MR, Poirier SE, Maskeri MM, Twining RC, & Gilmartin MR *Marquette*
Sex-specific modulation of trace fear learning, but not working memory, by pituitary adenylyl-cyclase activating-polypeptide (PACAP) signaling in the prefrontal cortex. Women are more than twice as likely as men to develop post-traumatic stress disorder (PTSD), yet the neurobiological basis of this sex difference is unknown. Recently, pituitary adenylate cyclase activating-polypeptide (PACAP) signaling has been implicated in PTSD in females: a single nucleotide polymorphism in the gene encoding the PACAP type-1 receptor (PAC1R) is associated with PTSD diagnosis and symptom severity in women but not men (Ressler et al., 2011). PACAP is a highly conserved peptide important for mediating adaptive stress responses, and dysregulation of PACAP may contribute to maladaptive stress in PTSD. Aberrant PACAP signaling may also contribute to PTSD through modulation of emotional learning. The PAC1R genetic polymorphism is associated with increased reactivity of fear circuitry to threat-related cues and impaired discrimination of threat and safety cues (Ressler et al., 2011, Stevens et al., 2014). Very little is known about how PACAP signaling normally participates in learning and memory, and previous work has focused primarily on male subjects. Here we examined the contribution of PACAP signaling in the prelimbic area of the prefrontal cortex of female and male rats to the acquisition of trace fear conditioning, an associative learning paradigm that requires the prefrontal cortex for cue maintenance during learning (Gilmartin et al, 2013). Adult Long-Evans rats received injections of the PAC1R antagonist PACAP6-38 (1, 2, or 3 mM, 0.5uL) into the prelimbic prior to trace conditioning. We found that blocking PAC1R signaling in the prelimbic during training impaired the formation of memory to the CS, but not context, selectively in females. Prelimbic PACAP6-38 did not impair performance in a delayed alternation working memory task, suggesting that prefrontal PAC1R effects on memory may be specific to emotional learning. These results provide support for a sex-specific role of PAC1R signaling within the prefrontal cortex in emotional memory formation.

Krasne FB[1], Bernier B[2], & Drew M[2] [1]*UCLA,* [2]*U Texas*
The dentate gyrus is important to both encoding and recall of hippocampal representations It is generally agreed that dentate gyrus (DG) plays a central role in establishing sparse, relatively non-overlapping hippocampal representations for newly experienced multi-attribute stimuli ("encoding"). However, DG's role in activating already established representations is uncertain. Theoretical considerations have led both to the conclusion that DG should and should not play a role in recall (Treves & Rolls, 1992; O'Reilly & McClelland, 1994; Krasne, Cushman, & Fanselow, 2015). Attempts to resolve this matter experimentally utilizing context fear conditioning have provided what seem to be conflicting results. E.g. Substantially depressing DG activity optogenetically during recall has no effect, but selectively depressing many fewer cells that were active during encoding attenuates fear. Partially depressing DG during encoding reduces fear at testing, but totally depressing it does not (Denny et al., 2014; Drew et al, in prep; Kheirbek et al. 2013; Nakashiba et al., 2012). We show here that such seemingly contradictory findings are in fact all consistent with a fairly conventional conception of hippocampal circuitry in which hippocampus forms representations of newly experienced contexts that become associated with fear in the amygdala and in which, during recall, cortically encoded information about contextual attributes reaches CA3 via potentiated synapses of both the direct EC-CA3 and the indirect EC-DG-CA3 pathways. These results can all be simulated with BACON, a biologically plausible model of context fear conditioning (Krasne, Cushman, & Fanselow, 2015), if it is assumed that optogenetic suppression interferes with development of Hebbian potentiation in DG during encoding. BACON cannot reproduce these results if the DG is not allowed to participate in recall. *Supported in part by R01MH102595*

Kutlu MG, Connor D, Tumolo JM, Garrett B, & Gould TJ *Penn State*
Nicotinic acetylcholine receptors modulate contextual fear extinction through ventral hippocampal GABAergic signaling Anxiety and stress disorders, which affect approximately 30% of the US population, are a cluster of crippling psychological disorders characterized by maladaptive anxiety and fear regulation and symptoms such as intrusive memories, hyperarousal, and avoidance. Numerous studies have attributed the psychopathology of anxiety and stress disorders to maladaptive behavioral responses such as an inability to extinguish fear. While exposure therapies are mostly effective in treating these disorders by enhancing extinction learning, relapse of anxiety disorder symptoms is common. Therefore, understanding neural substrates of fear extinction is imperative for developing more effective therapies for anxiety and stress disorders. Although several studies indicated a role for cholinergic transmission and nicotinic acetylcholine

receptors (nAChRs) in anxiety and stress disorder symptomatology, very little is known about the specific contribution of nAChRs in fear extinction process. Nevertheless, previous studies from our laboratory showed that acute nicotine, an agonist of nAChRs, impaired contextual fear extinction and this effect required high-affinity Îś4Îš2 nAChRs (Kutlu & Gould, 2014; Kutlu et al., 2016). In the present study, first, we examined the involvement of several brain regions key for fear extinction (i.e., dorsal and ventral hippocampus, dHPC and vHPC; ventromedial prefrontal cortex, vmPFC; basolateral nucleus of the amygdala, BLA) using c-fos immunohistochemistry and local drug infusions in C57BL6/J mice. Our results showed that systemic administration of nAChR agonist nicotine (0.18 mg/kg) during contextual fear extinction increased c-fos expression in the vHPC and BLA while not affecting dHPC and vmHPC c-fos levels. In line with these results, local nicotine infusions (0.35 Âţg/0.50 Âţl min/side) into the vHPC, but not dHPC, resulted in impaired contextual fear extinction. Interestingly, we found that local nicotine infusions into the vmPFC also resulted in impairment of contextual fear extinction, suggesting that the vmPFC nAChRs may be sufficient but not necessary for contextual fear extinction. Second, in order to elucidate the neurobiological mechanism underlying the nicotine-induced augmentation of vHPC activation, we ran western blots to test for the protein levels of the GABA synthesizing enzymes GAD65 and GAD67 in the dHPC and vHPC during contextual fear extinction. Our results showed that in the group that received acute nicotine (0.18 mg/kg) both GAD65 and GAD67 protein levels were downregulated in the vHPC but not in dHPC during contextual fear extinction compared to saline controls. This suggests that the nicotine-induced increase in c-fos expression in the vHPC may be a result of reduced GABAergic signaling and disinhibition of excitatory pyramidal neurons. Finally, using acute systemic injections of the Îś4Îš2 nAChR antagonist dihydro-beta-erythroidine (DhÎšE; 1 and 5 mg/kg) and Îś4Îš2 nAChR partial-agonist Sazetidine-A (0.01 and 0.1 mg/kg), which effectively desensitizes nAChRs without activating them, we examined the effects of nAChR inactivation on contextual fear extinction. Our results showed that in contrast to nicotineâĂŹs effects, deactivation and desensitization of nAChRs enhanced contextual fear extinction. Overall, our results suggest that vHPC nAChRs may be critically involved in contextual fear extinction by modulating GABAergic transmission. Our results also indicate that pharmacological interventions deactivating high-affinity nAChRs may help with anxiety and stress disorder symptomatology by augmenting fear extinction. *This work was funded with grant support from the National Institute on Drug Abuse (T.J.G., DA017949)*

Laborda MA, Mallea J, & Miguez G *U Chile*

Inhibitory potential of the extinction context is impaired by context exposure after but not during extinction training Two experiments evaluated the inhibitory potential of the extinction context and how this potential can be affected by exposure to the context alone. A first, previous, experiment, presented subjects with a CS followed by a mild foot shock in one context, following by extinction of this association in a different context with a 6s ITI. After the extinction phase, half of rats were exposed to the extinction context while the other half were just handled. Rats were tested for responding to the target CS in the extinction context, the context in which another CS was extinguished, and in a neutral but familiar context. Results showed that the extinction context passed a summation test, and that this inhibitory potential was impaired by exposure to the context alone. A second experiment evaluated if this impairment also occur when the context is exposed during the ITIs in the extinction phase instead of in a different phase. Two groups of rats received pairings of a target CS with a foot shock in one context and then extinguished in a different context. One group receive extinction with 6s ITIs while the other group received extinction with a 600s ITIs, allowing the exposure of the context alone for long periods of time. Finally, subjects were tested for responding to the target CS and another excitatory CS in the extinction context, and in a neutral but familiar context. Results showed that the extinction context passed a summation test, but this potential was not impaired by context exposure during the ITIs in extinction. It is possible that context exposure after the inhibitory training affects the inhibitory potential as an extinction process while exposure during inhibitory training acts as partial reinforcement, maintaining the expression of the inhibitory potential. *Fondecyt #1160132*

Lacagnina AF, Wright AJ, Ayoub A, Denny CA, & Drew MR *U Texas*

Spaced context exposure enhances context fear memory and hippocampal context coding Spaced training is superior to massed training in many learning paradigms. Although the spacing effect has been studied in in vitro hippocampal preparations, its mechanisms in mammals in vivo are not well understood. We examined the effects of spaced versus massed context exposure in one-trial contextual fear conditioning (CFC), a hippocampus-dependent learning paradigm that depends on two learning processes: 1) forming a mental representation of the context and 2) associating that representation with an aversive stimulus. Theories of CFC posit that such mental representations can be acquired during passive exploration of an environment and are essential for conditioning but do not make strong predictions about how varying the interval between context preexposure and conditioning will affect learning. Because the two learning processes can be separated in time, we predicted that introducing a delay between context preexposure and conditioning would strengthen CFC. We found that context preexposure 1, 4, 24 or 72 h before single-shock CFC produced stronger conditioned fear than did preexposure 1 min before or without

preexposure. A series of behavioral experiments revealed the effect of spaced context exposure was not explained by (1) a change in the susceptibility to extinction, (2) artifacts related to experiencing a novel context prior to conditioning, or (3) modulation of memory retrieval by primacy or recency. The results instead suggest that spaced context exposure strengthened context fear memory. To understand the neural activity patterns corresponding to the stronger conditioned fear following spaced preexposure, we used the Arc-CreERT2 x ChR2-eYFP activity-dependent neuronal tagging transgenic mouse line to compare the neuronal ensemble active during CFC acquisition with the ensemble active during retrieval. Transgenic mice received massed or spaced preexposure prior to single-shock CFC. Mice received an injection of 4-hydroxytamoxifen prior to CFC acquisition, thereby labeling neurons active during CFC acquisition with eYFP. Five days later, mice were re-exposed to the shock-paired context and euthanized 90 min later. We compared neurons active during acquisition (eYFP+) to those activated by memory retrieval (cFos+). Mice that received spaced preexposure displayed an increased percentage of reactivated (co-labeled) cells in CA3 but not the dentate gyrus as compared to mice receiving massed preexposure. In summary, spaced context exposure enhances CFC acquisition and increases the reactivation of CA3 neural ensembles associated with acquisition. These data demonstrate that trial spacing can modulate CFC and identify a neural correlate of the spacing effect in hippocampal CA3 related to memory strength. *NIH F31MH111243-01 & NIH T32MH106454-1*

Lamoureux JA, & Simard, AA *Boston College*

The Effects of Extinction and Counterconditioning on Negative Evaluative Conditioning in the Picture-Picture Paradigm The food-body, picture-picture paradigm represents a specific form of evaluative conditioning (EC) in which images of various food items serve as conditioned stimuli (CSs), shown in sequential pairings with images of different body types, which serve as the unconditioned stimuli (USs). Lascelles, Field, and Davey (2003) previously showed that pairing such food CSs with non-preferred body USs—specifically, those of obese individuals—results in negative evaluative conditioning. Importantly, later research suggested that this particular form of negative EC might not be affected by typical extinction procedures (Dwyer, Jarratt, & Dick, 2007). The present study was designed to replicate these claims and to additionally assess whether counterconditioning of the CSs could reverse the negative EC. Ninety-six participants were tested in either extinction or counterconditioning procedures; each received initial picture-picture EC in which food images were immediately followed by images of bodies. Some bodies were of average body mass index (BMI) range and were rated relatively positively by subjects, while other bodies were clinically obese, rated very negatively, and supported negative conditioning. Afterword, participants received either extinction training in which the food images were presented repeatedly in the absence of bodies, or counterconditioning in which foods were followed by pictures of preferred, average BMI bodies. The data replicated previous work: EC was not reversed by extinction. Similarly, counterconditioning produced only insignificant changes in ratings, albeit with a substantial trend toward significance. In future experiments, we will use more positively-valenced USs—images of extremely attractive bodies—to determine if the most appetitive of USs are able to reverse EC in this paradigm.

Latsko ML, & Jasnow AJ *Kent State*

Deficits in adult social behavior caused by periadolescent social defeat are ameliorated by corticosterone. Social defeat in adults typically results in two phenotypic responses during an immediate social interaction test: social approach (resistance) and social avoidance (susceptibility). The current study examines the impact of periadolescent social defeat on immediate and adult social behavior and neuroendocrine function in male C57BL/J mice. Initially, periadolescent mice are all resistance to the effects of social defeat; all display normal levels of social interaction. However, when tested again in adulthood, resistance and susceptibility emerge. A repeated analysis of corticosterone revealed that adult resistant mice had elevated corticosterone following the periadolescent social interaction test, suggesting that early increases in corticosterone may shape adult social behavior. To test this hypothesis, and to determine critical timing of corticosterone during periadolescence we administered corticosterone after the social interaction test (i.p 20 mg/kg) or after adolescent social defeat (400 μ/ml in drinking water). Corticosterone administered after the periadolescent social interaction test had no effect on adult social behavior. However, post-defeat corticosterone promoted increased social interaction in adulthood. To further characterize the effects of corticosterone on adult social behavior we administered Metyrapone (Corticosterone synthesis inhibitor; 100 mg/kg IP injection) during periadolescent social defeat. This manipulation, however, did not reduce social interaction any further than social defeat alone. Experiments are now examining if Mifepristone (Corticosterone receptor antagonist; 100 mg/kg IP injection) administered during periadolescent social defeat will block the pro-social behavioral effects of periadolescent corticosterone administration. Given these data, we hypothesize that corticosterone secretion following periadolescent social defeat during a limited time period may influence the development of neural circuits involved in regulating adult social behavior. *Farris Family Award & Whitehall Foundation Grant to AMJ & Judie Fall Lasser Award to MSL*

Lattal M *OHSU*

The baseline problem in associative and neurobiological studies of learning A fundamental issue that drives research

on basic learning and memory processes is determining how an experience at one time point impacts behavior during an assessment some time later. At a theoretical level, the challenge is to determine how the experience that causes learning is translated into performance during that assessment. Theoretical treatment of this learning-performance problem ranges from theories that explicitly ignore performance to theories that try to quantify the rules of performance. Understanding the relation between learning and performance becomes complicated when there are differences in baseline behaviors between experimental groups. I will discuss how the baseline problem complicates interpretations of performance in three areas: (1) when there are differences between context-evoked behaviors, (2) when there are differences in behavior before or after an experimental treatment, and (3) when genetic differences lead to differences in performance.

López-García P, & Sánchez-Carrasco L *UNAM*
Is resurgence affected by the reinforcement context? Resurgence refers to the recovery of an extinguished response (R1) when a response (R2) that replaced it is also extinguished. Nowadays, there are several explanations for this phenomenon (i.e. the response prevention theory, the extension of behavioral momentum theory, and the contextual account or resurgence). This experiment was designed to test the contextual account of resurgence, three groups of rats were trained in an instrumental conditioning procedure. During the first phase, lever pressing to Lever 1 (L1) was reinforced under a VR 16 schedule during twelve sessions. In phase 2, responding to L1 was extinguished, while groups received different rates of reinforcement (i.e., RF20, RF60, and RF60+TF30s) for pressing Lever 2 (L2). Finally, during the test session responding to both levers was extinguished. Findings showed the resurgence of responding to L1 only in the group RF20. These results are analyzed concerning the contextual account of resurgence. *DGAPA-PAPIIT 305815*

Lupkin SM, Lerner I, Sinha N, Tsai A, & Gluck MA *Rutgers*
Trait-like variations in rapid-eye-movement sleep modulate hippocampus-amygdala connectivity during fear conditioning Sleep, and particularly rapid-eye movement sleep (REM), has been implicated in the modulation of neural activity following fear conditioning and extinction in both human and animal studies. To date, though, no studies have demonstrated the potential effects of sleep prior to conditioning on subsequent neural activity during conditioning. Further, existing studies on sleep-conditioning relations are typically restricted to analyzing the effects of a single night of sleepâĂŤthus assuming a state-like relationship between the two. However, as shown in a recent study by our lab, long-term trait-like differences in sleep patterns across subjects are more predictive of subsequent performance in an emotional cognition task than sleep on any given night. To address these issues, we utilized long-term mobile sleep monitoring and functional neuroimaging to explore whether trait-like variations in sleep patterns, before fear conditioning and extinction affect patterns of neural activity during the conditioning and extinction procedures. Our results indicate that, in fact, trait-like levels of REM sleep strongly predict the strength of the connection between the hippocampus and the amygdala during conditioning. Such insights may provide a new understanding of the role that sleep plays in the neural underpinnings of anxiety disorders, such as phobias, which are intimately linked to conditioned fear and, as a result, may lead to the development of new treatments. *This work was supported by NSF/BCS grant # 1461009*

Lynch J, Grissom NM, McKee SE, Schoch H, Walsh L, Marini M, Nickl-Jockschat T, Reyes TM, & Abel T *U Penn*
Deficits in goal-directed learning are common to multiple mouse models of autism Autism Spectrum Disorders (ASDs) are a set of neurodevelopmental disorders that cover a wide range of symptomology including decreased striatal activity to reward. The overall prevalence of ASDs has increased and is 4 times more common in males than females. Given the role of striatal deficits in ASDs and the large discrepancy in prevalence rates, the current experiments assessed 3 different genetic mouse models in striatal-dependent goal-directed learning. The mouse models included 16p11.2 microdeletion animals, which is the most common genetic link with ASD, CNTNAP2 knockout animals, and Shank3b knockout animals. Animals were trained in a fixed ratio operant task where nose-pokes elicited a liquid reward. In all 3 models, experimental males displayed deficits in instrumental learning compared to wildtype (WT) animals, demonstrating impairments in goal-directed learning. Additionally, male 16p11.2 microdeletion animals had reduced motivation as measured by a lower breakpoint in progressive ratio testing. In contrast, only female Shank3b knockout animals had impairments in instrumental learning and no genetic model had impaired motivation. Overall, these findings suggest impaired goal-directed learning in males of 3 different ASD-linked genotype mouse models, and only the 16p11.2 model had deficits in motivation. Together, these data suggest that striatal dysfunction is a common mechanism contributing to male-specific increase risk for ASDs. Determining the mechanisms for these dysfunctions and understanding the sex-specific nature of these deficits are promising avenues for developing specific, targeted therapeutics for ASDs and other neurodevelopmental disorders. *Supported by the Simons Foundation Autism Research Initiative*

Malvaez M, Greenfield VY, Matheos DP, Angelillis NA, Wood MA, Kennedy PJ, & Wassum KM *UCLA*
A molecular brake on habit Optimal behavior and decision making result from a balance of control between two systems, one cognitive and one habitual. These systems rely on the dorsomedial (DMS) and dorsolateral (DLS) stria-

tum, respectively. But little is known about the molecular mechanisms required to establish and transition between each behavioral control system. Here we examined the role of one epigenetic mechanism, histone modification via histone deacetylases (HDACs), in this process. HDAC inhibition immediately following instrumental (lever press → reward) training increased histone acetylation throughout the dorsal striatum, altered transcription of key plasticity genes, and preferentially accelerated habit formation. Decreasing HDAC3 function, either by selective pharmacological inhibition or expression of a dominate-negative mutated HDAC3, in either the DMS or DLS also potentiated habit formation, while HDAC3 overexpression in either region prevented habit formation. These data identify a critical molecular substrate of the transition to habit, demonstrating HDAC3 to be a vital negative regulator.

Marton TM, Cavanaugh AR, Jin M, Ottenheimer D, & Hussain Shuler MJ *Johns Hopkins*
The cost of time: Background reward rate affects temporal decision making. We present evidence that the background reward rate of an environment is not only a critical variable in temporal decision making, but a useful tool for revealing an animal's understanding of the probability distribution of temporal intervals at which reward is predicted. First, we propose a theory whereby the subjective value of a reward enables a strategy approximating the maximization of the rate of reward accumulation. In particular we propose that a version of the equations: subjective value = reward - opportunity cost, and, opportunity cost = reward rate * time invested, is approximated by mice when making decision about how to allocate time. Thus, when an environment's background reward rate increases, opportunity costs increase, time becomes more valuable, and rewards at longer delays become less preferred. We then present two behavioral assays illustrating the predicted effect of background reward rate on temporal decision making: 1) an intertemporal choice task, in which mice choose between a small reward available after a short delay and a large reward available after a long delay, and 2) a give-up time task, in which reward is only delivered following a probabilistic temporal distribution. In the intertemporal choice task, preference for the larger-later reward option switches to the smaller-sooner option when the background reward rate is experimentally increased. In the give-up time task, because the probability of receiving reward decreases gradually as time passes, mice can optimize reward accumulation by exiting the reward port at a specific time, a time that is shown to decrease with increasing background reward rate, as predicted. The distribution of port exit times across background reward rates reveals the animal's representation of the probability distribution of temporal intervals at which to expect reward.

Matell MS, De Corte BJ, Della Valle RB *Villanova*
Attribution of a common cause for shifts in reinforcement intervals One of the first pieces of evidence suggesting a centralized, amodal, temporal memory system came from an experiment in which rats were trained using the peak procedure that a tone and a light each predicted reinforcement availability after 40s (Roberts, 1982). After shortening the tone-food interval to 20s, testing the temporal expectation associated with the light revealed a leftward shift in timed responding as well. Roberts (1982) interpreted this result as indicating that the auditory and visual systems share a common (i.e., amodal) memory store. We tested the alternative interpretation that rats attribute changes in one cueâĂŹs duration as resulting from a common moderating cause. In three experiments using the peak procedure, rats were initially trained that a cue A (e.g., tone) predicted reinforcement availability at 8s, whereas cue B (e.g., light) predicted reinforcement at 16s (counter-balanced). Then, we changed one cueâĂŹs onset-to-food availability interval during phase 2 (e.g., 8 → 4, 16 → 32, 8 → 12), and found equivalent directional shifts in the other cueâĂŹs production at test in phase 3. In a fourth experiment, phase 2 re-training was conducted in a novel context. We found that the magnitude of the phase 3 shift was substantially larger when we tested rats in the novel context compared to the original training context. Together, these data suggest that rats attribute a common, context-based cause to changes in temporal expectations.

McGann JP, Czarnecki LA, Kass MD, Fast CD, & Rosenthal MC *Rutgers*
Learning and expectation shape olfactory input to the mouse brain Sensory signaling in the brain is shaped not only by the external stimulus but also by the organism's previously-learned knowledge about the sensory world. This knowledge includes not only non-associative information about the natural statistics of the environment but also associative information about the significance of particular stimuli and the relationships among sensory stimuli within and across sensory modalities. By using this knowledge, a sensory system can potentially adapt to different circumstances by incorporating learned expectations into its analysis of ongoing sensory input. We use the mouse olfactory system as a model for exploring these phenomena because the initial convergence of top-down and bottom-up circuitry occurs in the olfactory bulb, where powerful genetic and optical tools make it possible to directly observe changing representations of olfactory stimuli in awake animals. We find that learned expectations about the sensory world are incorporated into olfactory processing surprisingly early in the system, including the circuitry of olfactory bulb glomeruli and even the olfactory sensory neurons, which transduce odorants in the nose and send their axons to the brain. Olfactory sensory neurons (Kass et al. 2013 in Science) and local inhibitory interneurons become selectively and persistently hyper-responsive to odorants that predict an impending footshock after Pavlovian fear learning, and the odor-specificity of this plasticity appears

to mirror the animal's generalization across odors. Passive statistical learning paradigms demonstrate that establishing and violating expectations about sequences of unreinforced stimuli can strongly impact the early olfactory system's response to odors. Recent data suggests that some of these phenomena could be mediated by a central amygdala → locus coeruleus → olfactory bulb circuit. The incorporation of predictive stimulus contingency information into very early sensory processing is unexpected and may help to relate sensory processing to higher-level cognitive functions like attention and memory retrieval. *This work was funded by grants from NIMH and NIDCD.*

Miguez G, Alfaro F, Canete A, Mallea J, & Laborda MA *u Chile*

Assessing Retrospective Revaluation of the Blocking of Occasion Setter Two experiments assessed the retrospective revaluation of the blocking of an occasion setter, in an appetitive head entry task. The blocking of an occasion setter (OS) refers to the reduction of the modulatory potential of a cue to a target CS, due to it being trained in compound with another cue that is already an occasion setter of the target. The retrospective revaluation of a blocked cue happens with additional presentations of the blocking cue alone (i.e., extinction), observing a recovery of responding to the blocked cue, when tested. Experiment 1 was designed to extinguish a positive OS, after it blocked another positive OS, to try to recover its modulatory potential, mirroring Pavlovian blocking. Results show blocking of the OS, but no retrospective revaluation, most likely due to the extinction of the OS phase design, which had presentations of the OS and the target cue with no reinforcement. Experiment 2 changes this phase to add reinforced presentations of the target CS with no OS, diminishing the blocking OS modulatory capacity, without extinguishing the target CS, maintaining its contingency with the reinforcement. Results are discussed focusing on the analogies between occasion setters and traditional Pavlovian CSs.

Monk KJ, Dzaringa B, & Hussain Shuler MG *Johns Hopkins*

The role of inhibition in cortical representations of cued temporal intervals When an animal learns that a light stimulus predicts a water reward at a specific temporal delay, neurons in primary visual cortex represent this delay. The process by which neurons change their responses to reflect cued-interval timing is referred to as âĂIJreward-dependent plasticityâĂİ, and previous studies have shown that acetylcholine (ACh) is a necessary and sufficient reinforcement signal for this to occur. Cued-interval timing can be modeled using a recurrent network of excitatory cells and broad, sparse inhibition. The model makes specific predictions about the role of inhibition in cued-interval timing; however, it does not take into account specific knowledge about the inhibitory subtypes which comprise the inhibitory microcircuit within visual cortex. Recent work has proposed the roles that these subtypes play in forming responses to visual cues, but it is unclear how the activity of these subtypes can lead to the acquisition and production of cued-interval timing. Here we investigate this question by using a combination of optogenetics and electrophysiology. For this study, we have used transgenic animals which express the light-activated cation channel, channelrhodopsin (ChR2), exclusively in parvalbumin-containing (PV+) inhibitory interneurons. Animals were implanted bilaterally with recording microelectrodes that were coupled to an optical fiber allowing for both electrophysiological recording and optogenetic activation of ChR2. Daily sessions of conditioning were performed such that a visual stimulus predicted a water reward by 1500ms. Prior to each session, 1ms pulses of laser light were used to optogentically identify PV+ interneurons. After the animal showed behavioral evidence of learning the task, we briefly activated PV+ cells within the temporal delay. Through these recordings we have found that PV+ cells are able to represent the temporal delay and when they do, they represent it as a sustained increase of activity following the light stimulus, returning to baseline at the time of expected water delivery. Furthermore, optogenetic activation of PV+ activity shifts the neural representation of time in non-PV cells to an earlier temporal interval. Both of these results corroborate the predictions of our computational model. Interestingly, we found that continued use of optogenetic perturbation may result in a secondary conditioning to this new temporal interval (i.e. PV+ neuron activation may be able to act as a reinforcement signal in visual cortex). Future studies will investigate the interplay of ACh release and PV activation as well as investigate the role of other cortical inhibitory interneurons (e.g. SOM+ and VIP+) in reward-dependent plasticity.

Morrison FG, Dias BG, & Ressler KJ *Emory*

Structural, functional and epigenetic responses to olfactory fear conditioning in mice Olfactory sensory neurons (OSNs) within the main olfactory epithelium (MOE) provide a rich model to study the perception of external cues and the underlying mechanisms regulating structural plasticity within the olfactory system. Using the M71-LacZ mouse line, we have previously demonstrated an increased number of M71+ OSNs in the olfactory epithelium and increased M71+ glomerular area in the olfactory bulb (OB) following cue-specific Pavlovian olfactory fear conditioning to acetophenone, an odorant shown to specifically activate the M71 receptor. Functionally, mice exhibit enhanced freezing to the conditioned odor stimulus following olfactory fear conditioning. We sought to determine whether the behavioral and structural changes observed after olfactory fear conditioning may be reversed with extinction training. Using native chromatin immunoprecipitation (N-ChIP) protocols on the MOE, we investigate the dynamic alterations in histone marks around the M71 gene locus following

both olfactory fear acquisition and extinction. Male mice were trained to associate mild footshocks with acetophenone. Three weeks after the last conditioning session, animals were handled only or exposed to an extinction session and 3 weeks after the last extinction session, animals were sacrificed. Extinction training specific to the conditioned odorant cue reversed the conditioning-associated increases in freezing and M71-specific OSN number and glomerular area. We also demonstrated a dynamic regulation of histone marks around the M71 locus associated with both cue-specific fear learning acquisition and extinction. Our observations shed light on how the olfactory sensory system responds dynamically to Classical Conditioning approaches with both fear and extinction learning. *Research supported by the following sources of funding: the National Institutes of Mental Health (1R01MH096764),Ruth L. Kirstein National Research Service Award (NRSA) Predoctoral Fellowship F31 MH105237-01, the Office of Research Infrastructure Programs/OD P51OD011132 [formerly National Center for Research Resources (NCRR) P51RR000165].*

Moscarello J & LeDoux JE *NYU*

Investigating the associative structure of active avoidance memory In signaled active avoidance (SigAA) behavior, a response performed during a CS prevents the delivery of an aversive US. Longstanding ambiguity surrounding the relevant learning mechanisms has caused SigAA to fall out of favor among researchers. However, more recent innovations in learning theory allow for a fresh perspective on the conditioning processes underlying SigAA. For instance, instrumental contingency degradation paradigms have been used to establish the associative link between an action and the outcome it produces. By adding disjunctive reinforcement, in which the reinforcing outcome occurs in the absence of the action that usually precedes it, a previously acquired action-outcome association can be degraded. We adapted this paradigm to test whether SigAA requires an action-outcome association. In our two-way shuttling procedure, subjects learn to cross a divided chamber during an auditory CS in order to cause the omission of an aversive US, which is replaced with a blinking light confirmation signal. We trained subjects in this SigAA paradigm before breaking them into full and degraded contingency groups. The full contingency group continued with normal avoidance training. The degraded contingency group could always avoid the US by shuttling. However, if subjects in this group failed to shuttle, there was a 2/3 probability that the US would be omitted and replaced with the confirmation signal (i.e. disjunctive reinforcement). In a reinforcer-free (CS only) test, this degraded contingency treatment significantly decreased shuttling relative to the full contingency group, and caused an increase in Pavlovian freezing. Notably, freezing among degraded contingency subjects was comparable to poor avoiders that never displayed the avoidance response. These results constitute novel evidence that SigAA behavior depends on an action-outcome association.

Narayanan NS, Emmons EB, DeCorte B, Kim Y *U Iowa*

Ramping neurons in corticostriatal neuronal ensembles during interval timing Neurons in the prefrontal cortex and the striatum powerfully control the timing of movement. We record from neuronal ensembles in rodent prefrontal cortex and striatum during a fixed interval-timing task. We find that ramping activity is the most common pattern of neuronal activity among corticostriatal neurons. In the prefrontal cortex, ramping activity requires D1-type dopamine receptors, and stimulation of neurons expressing D1-type dopamine receptors can increase ramping in prefrontal ensembles. In the striatum, ramping activity more strongly predicted elapsed time than in prefrontal cortex. Striatal ramping neurons had strong correlations with prefrontal ramping neurons and were coherent with stimulus-triggered 4-Hz prefrontal oscillations. Finally, we found that prefrontal inactivation attenuated ramping activity in striatal neurons, indicating that striatal ramping requires prefrontal input. These data indicate that ramping activity is a prominent pattern of temporal processing among corticostriatal ensembles, providing some insight into how neurons might influence the timing of movements.

Navarro VM, Wasserman EA, McMurray B, & Roembke, TC *U Iowa*

The role of negative associations in learning rich associative networks Adaptive behavior is generally thought to result from both positive (excitatory) and negative (inhibitory) forms of associative learning. Indeed, previous results have shown that, in a many-to-many learning task, pigeons make more correct responses if incorrect rather than extraneous options are available. Here, we extended those findings by using a task that promotes the learning of negative information (what not to peck) rather than positive information (what to peck). In a two-alternative, forced-choice task, we trained pigeons to learn an associative matrix between 16 object photographs and 16 colored tokens (pexigrams), using food as reinforcement for correct responses. During training, each of the objects had one of the pexigrams as its incorrect option. The development of positive associations was manipulated by restricting which pexigrams were available to be presented as correct options. Performance was later tested with two kinds of probe trials. On incorrect vs. extraneous trials, the correct option was replaced by an extraneous pexigram. On correct vs. extraneous trials, the incorrect option was replaced by an extraneous pexigram. We observed no significant reduction in the proportion of correct responses on incorrect vs. extraneous trials, and no bias to choose the previously trained, correct option on correct vs. extraneous trials. Thus, pigeons' responses were largely—if not completely—based on negative information. These results underscore the

role of negative information in the acquisition of complex associative matrices, and further support this methodology as a tool to study the dynamics between excitation and inhibition.

Nelson JB[1], & Lamoureux JA[2] [1]*U Basque Country;* [2]*Boston College*
The effects of extinction on context conditioning The attentional theory of context processing (ATCP e.g. Rosas & Callejas-Aguilera, 2006) assumes that attention to contexts is aroused by extinction. In two experiments we used the common assumption that attention modulates learning rates (e.g., Mackintosh, 1975; Pearce & Hall, 1980) to test the prediction that extinction will enhance the rate at which the context can subsequently be conditioned. In a video game, human participants reacted to colored sensors that predicted the appearance of an attacking spaceship against a background outer-space context by pressing a key on a keyboard to charge a weapon. All participants received conditioning with one sensor and then half the participants received extinction. All participants then received context-conditioning trials where unsignaled spaceships arrived on a variable 20-s interval schedule. Both groups learned to maintain keypressing during the inter-trial intervals, and there was no solid evidence that extinction facilitated that learning. In Experiment 2 the context conditioning was conducted on a fixed interval 20-s schedule. On test trials where the spaceship arrived every 60 seconds, there was evidence that subjects experiencing prior extinction learned to time the occurrence of the spaceship better than those that had not received extinction. Mechanisms responsible for the differences are discussed along with their implications for ATCP. *PSI2014-52263-C2-2-P from the Spanish Ministry of Science and Innovation and grant IT-694-13 from the Basque Government.*

Nentwig TB & Freestone DM *Bucknell*
(Mis)estimating the Fixed Interval Gradient The results of Fixed Interval experiments are usually presented in one of two forms. The first is the Fixed Interval gradient, which gives the moment-by-moment estimate of the response rate as a function of time, averaged over many trials. The second is the transition time, which gives a single-trial estimate of the time at which the rat transitions from a low to a high response rate. New methods of analyzing the Fixed Interval gradient require fitting models to the averaged data, and the quality of the fit determines the degree to which the parameters of the model are behaviorally informative. But even when a model may fit the gradient well, the parameters of the fit may not reflect the underlying single-trial data that makes up the gradient. And while there are several transition point algorithms that seem to provide an appropriate result, they are rarely validated against known transition times, and not compared with each other. Here, we explore non-parametric, maximum likelihood, and bayesian methods to fit the gradient, and to find the transition times. We simulated hundreds of thousands of Fixed Interval trials with known transition statistics, and evaluated the degree to which both transition analysis and fitting the averaged gradient can recover those statistics. We describe each method on accuracy, ease of use, and computational speed and complexity.

Ng K, Pollock M, Urbanczyk P, Woon E, & Sangha S *Purdue*
D1 receptor mediated signaling in the basolateral amygdala modulates safety-fear-reward cue discrimination Accurate discrimination among cues signifying danger, safety or reward initiates the proper emotional response in order to guide behavior. Since potentially rewarding and dangerous stimuli often occur simultaneously leading to opposing behaviors, reward- and fear-related circuits must interact in order to mediate these antagonistic behaviors. In order to investigate how the fear, safety and reward circuits integrate, we train Long Evans rats to discriminate among a) a fear cue paired with footshock, b) a safety cue in the presence of the fear cue resulting in no footshock, and c) a reward cue paired with sucrose delivery. A selective increase in freezing to the fear cue and reward seeking to the reward cue indicate good fear and reward discrimination, respectively. Using this task we have previously identified neurons in the basolateral amygdala (BLA) that discriminate among these cues (Sangha et al, 2013). Also within the BLA, dopamine levels increase during learned fear responses (de Oliveira et al, 2011) and D1 receptors are required for fear extinction (Hikind et al, 2008). Dopamine signaling is also implicated in discriminatory reward learning (Eagle et al, 2015). Based on this, we tested the hypothesis that fear-safety-reward cue discrimination requires D1-mediated dopamine signaling in the BLA. Systemic injections of a D1 receptor agonist (10mg/kg SKF-38393; n=8) disrupts both fear and reward discrimination compared to saline controls (n=12). When the D1 receptor agonist is infused directly into the BLA bilaterally (1.0 μg/0.5μL SKF-38393; n=9) 30 min prior to each discrimination session, fear discrimination, but not reward discrimination is again impaired compared to saline controls (n=10). Systemic injections of a D1 receptor antagonist (3.33μg/kg SCH-23390; N=7) only disrupts fear discrimination, but not reward discrimination compared to saline controls (n=12). When a D1 receptor antagonist is infused directly into the BLA bilaterally (0.25 μg/0.5μL SCH 23390; n =8), reward discrimination, and fear discrimination, are not different from saline controls (n = 10). Together, this indicates that 1) dopamine D1 receptor activity in the BLA is not necessary for reward discrimination, and 2) successful fear discrimination does not require D1 receptors in the BLA but overstimulation of the D1 receptors will impair fear discrimination.

Noble LJ, Meruva VB, Kilgard MP, & McIntyre CK *UT Dallas*
Vagus nerve stimulation reverses extinction impairments and alters PTSD symptoms in the SPS animal model Posttrau-

matic stress disorder (PTSD) can develop following a traumatic event. Symptoms of PTSD include hypervigilance, avoidance, and increased anxiety. Exposure therapy is a form of cognitive behavioral therapy that is commonly used to treat these symptoms. During exposure therapy, patients are repeatedly exposed to cues that remind them of the trauma until they learn healthier responses to those cues. However, PTSD patients show impairments in extinction learning, which may increase nonresponse rates and dropout rates. Adjuncts to exposure therapy could be utilized to increase the effectiveness by promoting successful extinction learning, this could lead to decreases in nonresponse and dropout rates. Vagus nerve stimulation (VNS) is an FDA-approved treatment for the prevention of seizures. VNS shows promise as an adjunct for exposure therapy because previous research indicates that it enhances memory consolidation in rats and in humans, and we recently found that pairing VNS with unreinforced exposures to a conditioned stimulus can enhance extinction learning and protect against relapse in the single prolonged stressor (SPS) rat model of PTSD that shows resistance to extinction. The current studies are designed to test the hypothesis that extinction impairments contribute to general symptoms of PTSD and, therefore, treatments that promote successful extinction should produce benefits that reach beyond the cue-induced fear. SPS and control rats were fear conditioned for two days, then given daily extinction training with VNS or sham stimulation. One week, and six weeks later, rats were given tests of hypervigilance (startle), avoidance (conditioned place avoidance), and general anxiety (elevated plus maze). We hypothesize that reversing extinction impairments in SPS-treated animals with VNS will decrease anxiety, avoidance, and hypervigilance. Results indicate that VNS pairing with extinction training brought fear expression in SPS-treated rats to control levels, and increased time spent in the open arms of an elevated plus maze (versus sham-treated SPS rats) one week after extinction training. These results suggest that VNS enhancement of extinction also provides benefits for additional PTSD symptoms seen in the SPS model. *DARPA ElectRx, SBIR, NIH*

Opendak MM, Wood K, Mansour R, Serrano P, & Sullivan RM *NYU*

Amygdala PKMzeta increases with the emergence of fear learning in infant rats During infancy, rapid learning associated with attachment and orientation to a caregiver is essential to survival. This developmental period also prevents the acquisition of avoidance learning. In rodent models, this developmental time window occurs prior to post-natal day 10 (PND 10), during which pups display heightened preference learning accompanied by decreased aversion learning. PND 8 rats presented with odor-shock pairings fail to avoid the odor associated with shock, and show a preference for the paired odor. Older pups (PND 12) given odor-shock pairings develop an aversion to the odor at subsequent test. One key developmental mechanism that appears to direct the change from a preference for the odor associated with shock to an aversion, involves the activation of the amygdala by corticosterone. Corticosterone is low in pups during the sensitive period and increases at PND 10. We investigated synaptic markers which may be important for establishing the avoidance memory and that are likely activated by corticosterone. Protein kinase M zeta (PKMζ), which is important for late-phase LTP and long-term memory, is also upregulated during stress (Sebastian et al 2013, PLoS One, vol 8, e79077). Therefore, we investigated the role of PKMζ in avoidance vs preference learning in rat pups using the paired odor-0.5mA shock fear-conditioning paradigm. Methods: PND 8 and PND 12 pups were given either paired (simultaneous odor and shock) or unpaired (shock 2 min after odor) training and tested 24hr later on a Y maze with one arm containing the conditioned stimulus (CS) odor and the other a familiar odor. Immediately after Y maze test, pups were sacrificed and amygdalae were harvested. The tissues were separated into cytosolic and synaptic cellular fractions. Each fraction was analyzed by Western blots. Separate groups of pups (conditioned at PN8 with and without CORT, PN12) received microinfusions of the PKMζ inhibitor ZIP or scrambled ZIP before Y maze testing. Results: Pups in the unpaired condition showed no preference for either arm. PND 8 pups in the paired condition preferred the CS odor and PND 12 pups in the paired condition avoided the CS odor ($p<0.01$). PND 12 in the paired condition had higher cytosolic PKMζ in the amygdala compared to unpaired pups ($p<0.05$) with no change in synaptic PKMζ. PN8 paired did not show any changes in cytosolic or synaptic PKMζ. Infusion of the PKMζ inhibitor ZIP into the amygdala before the Y maze blocked aversion in pups conditioned at PN12 and pups conditioned at PN8 following CORT administration. Conclusions: Increased PKMζ expression following the sensitive period plays a role in the activation process of the amygdala and the formation of aversive memories.

Ortiz S, Gilman TL, Cecil C, Immel ZJ, Adkins S, Huda R, Adkins JM, & Jasnow AM *Kent State*

Glutamatergic signaling in the nucleus accumbens modulates cued fear extinction The nucleus accumbens (NAcc) has primarily been studied as a locus mediating the effects of drug reward and addiction. This is due to the regionâĂŹs role of ascribing valence and salience to internal and external cues. In light of this central function, we sought to explore the influence of the NAcc on cued fear expression and extinction. Specifically, we examined the role of glutamatergic receptors in mediating these fear-related processes. Using adult male C57BL/6 mice, we stereotaxically implanted bilateral cannulae directed at the NAcc. Twenty-four hours following fear training to an auditory tone, we infused the AMPA antagonist NBQX or the metabotropic glutamate receptor class I (mGluRI) antagonist AIDA into the NAcc

5 min prior to expression testing/extinction training. Fear expression was significantly attenuated by NBQX infusion, whereas AIDA had no immediate influence on fear expression. However, when mice were tested 24 h later for extinction retention, those previously infused with AIDA exhibited enhanced fear, indicating AIDA had impaired the consolidation of fear extinction. Our data indicate ionotropic glutamatergic signaling in the NAcc is important for mediating behavioral fear expression. Conversely, metabotropic glutamatergic signaling appears critical for reassigning valence to a previously aversive cue (extinction). Future experiments will explore dopaminergic modulation of these glutamate receptor-mediated effects on fear processing. *This work was supported by the Whitehall Foundation.*

Ostlund SB *UC Irvine*

Dopamine and the transfer of motivational control over cue-triggered cocaine seeking It is widely believed that drug-paired cues have the ability to elicit compulsive drug seeking and relapse by triggering a dopamine-dependent state of heightened drug motivation or "craving." According to this view, cues associated with past drug use should be capable of instigating drug seeking even when they occur unexpectedly (e.g., independently of ongoing behavior) and do not directly signal a specific strategy, or habit, to obtain drugs (i.e., their influence should generalize to elicit new drug-seeking actions). Suitable methods for studying these important features of cue-triggered drug seeking in rodents have yet to be established. We have adapted a behavioral protocol that has been successfully used in studies on the motivational properties of natural-reward-predictive cues. Rats were trained to self-administer intravenous cocaine on two distinct discrimination tasks. While both tasks involved reinforcing rats with cocaine for performing a lever-press response during a discriminative cue, each task used a different cue and response (e.g., light→left press and noise→right press). Importantly, these tasks were initially trained in separate sessions in which only trials with the relevant (reinforced) cue-response contingency were included. However, subsequent tests sessions revealed that these cues were effective not only in invigorating performance of whichever action they were originally paired with during training, they also exerted an immediate excitatory influence over the alternative cocaine-seeking action. Interestingly, whereas systemic treatment with the broad-spectrum dopamine antagonist flupentixol dose-dependently suppressed cue-triggered cocaine self-administration, it had relatively modest effects on the transfer of discriminative control from one action to another. In contrast, an analogous study with food reinforcement found that the transfer of control between food-seeking actions was highly sensitive to dopamine receptor blockade. These findings raise important questions regarding the role of dopamine in cue-motivated cocaine seeking. *NIH/NIDA DA029035*

Palmisano AN, Hudd E, McQuade C, de Wit H, & Astur RS *U Connecticut*

Nicotine enhances responding for chocolate rewards In addition to its primary addictive properties, nicotine is believed to enhance the rewarding effects of other stimuli. We aimed to determine whether nicotine enhances the value of food rewards in a virtual reality conditioned place preference paradigm in humans. Undergraduate participants with varying levels of nicotine dependence were recruited for a 2-day study. On day 1, participants explored two virtual rooms where they received multiple pairings of real M&M rewards in one room, and no rewards in the other room, followed by a free-access test session with no rewards. On the second day, participants received multiple test sessions to assess extinction. Subsequently, participants received M&Ms in a novel context and were then tested for reinstatement. Prior to testing on each day, subjects were administered either nicotine (4 mg) or placebo lozenges. We found that there were no significant conditioned place preferences in time nor ratings between nicotine and placebo groups on Day 1. However, for participants who demonstrate some level of nicotine dependence, the previously-paired M&M room was rated as significantly more enjoyable for the nicotine group compared to the placebo group. On Day 2, no significant differences between treatments were found during the initial extinction sessions; however, those who received nicotine on Day 1 spent significantly more time in the previously-paired M&M room than did the placebo group during the last extinction session. Moreover, participants who received nicotine on Day 2 demonstrated significant reinstatement compared to placebo-treated participants. These findings provide insight into how nicotine dependence can be particularly resistant to treatment and also demonstrate the efficacy of utilizing a virtual conditioned place preference paradigm to help understand the behavioral mechanisms of substance dependence.

Parrish JN[1], Lam SY[1], Speth RC[2], & Torregrossa MM[1] [1]*U Pittsburgh;* [2]*Dept. of Pharmaceutical Sciences, Nova Southeastern University, Fort Lauderdale, FL*

Estradiol modulation of the renin angiotensin system and the regulation of fear extinction Low estradiol levels during fear extinction have been shown to impair extinction consolidation, resulting in increased fear expression during extinction recall in women and female rats. However, the mechanism by which this occurs has not been identified. Estrogen modulates the renin angiotensin system (RAS) by downregulating the hypertensive axis (including angiotensin II type I receptors; AT1R) and upregulating the antihypertensive axis of the RAS. Accordingly, our lab has found that systemic administration of the AT1R antagonist losartan prior to fear extinction enhances extinction consolidation and reduces fear expression during extinction recall in female rats with low estradiol levels. Next, we investigated potential mechanisms by which estradiol interacts with the RAS to enhance extinc-

tion consolidation. Adult female Sprague-Dawley rats received a 0.5mg/kg injection of levonorgestrel, a commonly used hormonal contraceptive (HC) that lowers circulating estradiol levels, or vehicle for 5 days. Rats were sacrificed, and blood and brains were collected for further processing. Estradiol and angiotensin II levels were measured in serum via enzyme immunoassay. Brains were sectioned (20μm) and mounted on slides and AT1R autoradiography was performed to compare AT1R binding between groups. In a separate cohort, brains were collected from rats treated with HC or vehicle. Tissue punches were taken from brain regions associated with fear, and qPCR was performed to compare AT1R mRNA expression between groups. Finally, another cohort of rats was run through a cued fear conditioning paradigm, and angiotensin II (30μg/kg) or vehicle was administered systemically before or immediately after the extinction training session in female rats with high estradiol levels. Extinction recall was tested 24 hours later. A t-test revealed that the HC treated group had significantly decreased levels of estradiol ($p < 0.001$) and significantly increased levels of angiotensin II ($p < 0.05$) compared to the vehicle treated group. No significant differences in AT1R expression or binding were found between HC and vehicle treated groups. Systemic angiotensin II had no effect on extinction acquisition. However, pre-extinction session treatment with angiotensin II produced a non-significant increase in freezing during extinction recall. In conclusion, angiotensin II, which is part of the hypertensive axis of the RAS and an agonist of the AT1R, was increased in rats with low estradiol levels, but there were no differences found at the receptor level. This suggests that extinction consolidation deficits in rats with low estradiol may be due to increased angiotensin II, but additional behavioral studies are needed to clarify this relationship. Understanding the mechanisms by which circulating hormones affect extinction learning could aid in the development of better treatments for people who suffer from anxiety disorders, such as PTSD. *K01DA031745, Pennsylvania Department of Health; R01MH077159*

Payne JW, Opara V, Petrov P, & Iordanova MD *Concordia*

The effects of a mixed extinction paradigm on the retrieval of previously reinforced Pavlovian associations Extinction and overexpectation are two paradigms, which lead to a reduction in the associative relationship between events. In extinction this is achieved through omission of the delivery of the expected outcome. In overexpectation two individually trained cues are presented together to generate an inflated expectation of the outcome. This inflated expectation is met with a delivery of a single outcome. The characteristic reduction in the conditioned response following extinction or overexpectation training reflects a reduction in the associative relationship between the target cue and the outcome. However, this reduction is easily disrupted: testing outside of the extinction context, letting time pass, or giving unsignalled exposure to the outcome, each lead to an increase in the conditioned response from extinction levels. Neurally, the reduction in associative strength seen during extinction and overexpectation training is tracked by unique and overlapping neuronal populations in the central nucleus of the amygdala. This raises the possibility that targeting the unique and common populations behaviourally i.e. through combining extinction and overexpectation training, might lead to lasting reduction in behaviour. To test this prediction, following conditioning of two individual cues with a reward, rats were assigned to either: blocks of overexpectation sessions followed by blocks of extinction sessions (mixed extinction), overexpectation sessions only, extinction sessions only, or a constantly reinforced control group. Subsequent renewal, spontaneous recovery and reinstatement tests show higher responding in the control group compared to the three groups that had undergone extinction or overexpectation training, with the mixed extinction group showing the lowest response. This effect was consistent across different dependant variables. These findings have potential implications for deepening reductions of maladaptive associations on behaviour, such as those present in addiction and anxiety disorders.

Pearce J *Cardiff*

A new look at an old theory Pearce and Hall (1980) proposed that associative learning with one or more stimuli will take place until the outcome that follows them can be predicted by the sum of their associative strengths. At this point, such controlled processing is replaced by automatic processing. Automatic processing allows the stimuli to elicit responses, but prevents them from undergoing further changes to their associative properties. The present talk will explore the merits of an alternative view of this interaction between automatic and controlled processing. Controlled processing is assumed to continue until any outcome that occurs is accurately predicted by a single stimulus. The successful stimulus will then receive automatic processing that not only enables it to elicit a response, but also prevents any stimulus that accompanies it from receiving controlled processing. The implication of these proposals for how the associative strength, and the associability, of a stimulus can be modified will be considered.

Polack CW, O'Hara S, & Miller RR *Binghamton*

Associative structure of inhibitory perceptual learning Exposure to a pair of stimuli that favors comparisons and contrasts yields an enhanced ability to discriminate between these stimuli. In previous experimental studies, two distinguishable stimuli X and A were each paired with a common stimulus B to create two compound stimuli XB and AB. It is of interest to investigate how an organism differentiates between XB and AB. Thus far, evidence suggests that unique features form mutually inhibitory associations. This was evidenced by pairing feature A with a biologically relevant stimulus (i.e., an unconditioned stimulus [US]) and

observing that stimulus X alone serves to inhibit anticipatory behaviors for that US. These observations may reflect the mutually inhibitory nature of the two features X and A. However, by assessing influence on the US rather than feature A, these experiments tested inhibition only indirectly. In the experiments presented here, a more direct measure of inhibition is proposed and tested. We find retardation and negative summation of associations between unique features X and A by assessing their ability to serve as competing cues during overshadowing treatments. Stimulus X was less susceptible to overshadowing by A (retardation) and was able to attenuate overshadowing by A of other stimuli when X was present at test, which is indicative of negative summation of a competing stimulus.

Pollack GA, & Bergstrom HC *Vassar*

Cued fear memory retrieval accuracy over time The ability to discriminate and generalize fear conditioned stimuli is adaptive in an ever-changing external environment. The passage of time is one important factor that can influence memory generalization. Fear conditioned contextual stimuli are well-known to generalize over time. Surprisingly little is known about the accuracy of fear conditioned auditory stimuli with the passage of time. Further, the brain-wide neuronal activity patterns underlying cued fear memory performance at very long time retention intervals following learning is relatively unknown. The present study sought to establish an auditory fear conditioned stimulus discrimination gradient at 1-day (recent) and 30-days (remote) following learning. Adult male C57BL/6 mice were fear conditioned with three auditory conditioned stimuli (CS; 75 dB, 5 kHz, 20 s) that each co-terminated with a foot shock unconditioned stimulus (US; 0.5 s, 0.6 mA) in context A. One day after fear conditioning, mice were presented with one of five tones at different frequencies (2, 3, 5, 8, or 12 kHz; 75 dB, 20s) in a novel context (context B). 30 days later, mice were returned to context B and replayed the tone. 60 min following the test, brains were processed for activity-regulated cytoskeletal associated protein Arc/Arg 3.1 immunohistochemistry. Results showed mice discriminated most (2, 3 and 12 kHz), but not all (8 kHz), auditory frequencies at the recent frame (24 hrs). Mice were still able to discriminate the same stimuli 30 days later, suggesting a high degree of accuracy for cued fear memory retrieval over time. In a second experiment, the tone (2, 3 and 5 kHz) was played at only the remote time point following learning. In contrast to the first experiment, results showed a flattening of the stimulus generalization gradient. Across both experiments, the target CS strength remained intact. Based on these results, we conclude that the sharpness of the remote auditory cued fear memory generalization gradient depends on whether or not the non-target stimuli were pre-exposed at a recent time point following learning. Brain-wide Arc/Arg 3.1 mapping is ongoing in the basolateral amygdala and prelimbic cortex. *We thank the Undergraduate Research Summer Institute (URSI) at Vassar College for funding this research.*

Poulos AM *U Albany*

The Developmental Progression of Contextual Fear Conditioning and its Underlying Neuroanatomical Pathways There is a growing body of research focused on the neural systems development of cognitive and affective learning. Particular attention has been paid to the emergence of contextual fear conditioning during infancy and the expression conditional fear responding during adolescence, yet there is paucity of available data, which extends across these developmental periods towards adulthood. The present talk describes recent results from our laboratory assessing across development: 1) the acquisition and long-term retention of fear responses in male and female rats 2) the functional status of key neuroanatomical amygdala afferents during the retrieval of contextual fear responses. Towards the latter, we assess fear evoked immediate early gene expression constrained to neuronal tract tracing of entorhinal and prefrontal cortical neurons projecting to the basolateral amygdala. *R03MH093781-03 (AMP), FRAP-A 900226-08 (AMP), SUNY Startup (AMP)*

Rankin C *U British Columbia*

Redefining habituation as a change in response strategy Traditionally researchers who study learning have focused on a single dimension of the behavior (i.e. response probability, duration or magnitude). Our high throughput behavioural analyses of habituation in C. elegans have changed this view. First we have shown that there are a number of independent components (habituation rate and final level for probability, latency, duration and speed) of habituation that can show different forms of plasticity and, for the most part, are mediated by different genes. In addition, the response does not occur in a vacuum- changes in ongoing behavior occur at the same time as the response decrement. Interestingly, as some aspects of behavior decrement others appear to sensitize. When these changes in the components of behavior are integrated it facilitates dispersal allowing the animal to move away from the stimulus. This offers a new way to think about the role of habituation and sensitization in the context of overall behavioral strategies. These findings also have implications for other response-based measures of learning and memory.

Regetz TK, Miller DP, Nilles KL, Cook-Snyder DR, & Servatius RJ *Rutgers*

Partial reinforcement during signaled lever-press avoidance training is less detrimental to learning in behaviorally inhibited Wistar-Kyoto rats compared to Sprague Dawley rats The behaviorally inhibited Wistar-Kyoto (WKY) strain has been studied extensively as a model for anxiety vulnerability. WKY rats acquire signaled lever-press avoidance more rapidly and they are resistant to extinguishing the avoidance response when compared to Sprague Dawley (SD) rats (e.g., Servatius et al, 2008). Recently it was demonstrated that

learning in behaviorally inhibited humans was less affected by partial reinforcement during Pavlovian eye blink conditioning (Allen et al., 2014). In the present study we compared avoidance acquisition in female WKY versus female SD rats receiving either 100% paired tone-shock trials, or 50% paired trials with 50% tone only trials. WKY rats receiving 100% paired trials showed the highest levels of acquisition. SD rats receiving 50% paired trials showed very little avoidance acquisition. WKY rats receiving 50% paired trials showed levels of acquisition similar to but slightly higher than SD rats receiving 100% paired trials. Our results suggest that female WKY rats are extremely influenced by the tone-shock contingency even when it is inconsistent. Such enhanced associative learning in vulnerable populations could be a major factor in the development of anxiety and stress disorders. To further study that relationship, we are performing ongoing immunohistochemical analysis in rat brain tissue from this study that aims to identify activated regions following avoidance training. *Stress and Motivated Behavior Institute, Syracuse VAMC*

Robinson-Drummer PA, Heroux NA, & Stanton ME *U Delaware*

Intra-medial prefrontal cortex antagonism of muscarinic acetylcholine receptors disrupts the context preexposure facilitation effect Cholinergic dysfunction following neonatal alcohol exposure contributes to learning impairments in juvenile rats tested in a variant of context fear conditioning known as the context preexposure facilitation effect (CPFE; Dokovna et al., 2013). Following alcohol exposure, cholinergic enhancement can mitigate both behavioral deficits in the CPFE (Dokovna et al., 2013) and neurological abnormalities in the brain (Monk et al., 2013; Otero et al., 2012), however the regional loci of these effects are still unclear. Previously, our lab has shown that dorsal hippocampal (dHPC) cholinergic function contributes significantly to learning impairments in the CPFE. Scopolamine, a muscarinic acetylcholine receptor antagonist, disrupts the CPFE in juvenile rats, when administered into the dHPC prior to preexposure, training or testing (Robinson-Drummer et al., 2016). The current experiment extended these findings by locally infusing scopolamine into the medial prefrontal cortex (mPFC) prior to all phases of the CPFE or prior to only a single phase. On PD 31, all rats were either preexposed to the training context (Pre group) or an alternate context (Alt –Pre group). Twenty four hours later, all animals were given two immediate 2s, 1.5mA shocks in the training context. Finally, twenty four hours after training, all animals were tested for freezing in the training context. Different groups of rats received bilateral infusions of scopolamine (35Îijg/side) or PBS 10min before preexposure, training, testing or before all three phases. A 2 (Drug) x 4 (Infusion day) design was used to create the Pre groups while the two Alt –Pre groups (PBS v scopolamine) were pooled across infusion day. Following infusions on all days, the Pre group given PBS exhibited significantly more fear to the training context than the Alt-Pre group given PBS or scopolamine and the Pre group given scopolamine suggesting that mPFC cholinergic function is necessary for successful CPFE performance. Analyses of the individual infusion days revealed no effect of scopolamine administered prior to testing and a main effect of scopolamine following preexposure infusions. A main effect of both scopolamine and preexposure condition on the training day suggests that mPFC cholinergic function may contribute to training day learning as scopolamine animals were significantly impaired relative to PBS animals. In total, these findings suggests a role of mPFC cholinergic function in contextual fear conditioning in juveniles that is dependent on the phase of conditioning in the CPFE paradigm. Enhancing cholinergic function in the mPFC and/or dHPC may reveal an interaction between these regions which contributes to deficits observed following neonatal alcohol exposure. *NIH grant R01 HD075066-01A1 to MES*

Rosenthal MC, Bacallao M, Kessler EM, & McGann JP *Rutgers*

Discriminative Olfactory Aversive Learning Induces Rapid Physiological and Perceptual Plasticity Associative mechanisms allow organisms to learn which stimuli in the environment predict danger. Such learning allows the brainâĂŹs sensory systems to increase their sensitivity to ecologically-critical stimuli or optimize discrimination between threat-predictive and neutral stimuli. Here, we used discriminative aversive conditioning in human subjects to explore these interactions between sensory processing and learning. Prior to conditioning we used a triangle task to assess each subject's ability to discriminate between a pair of very similar odorants and categorized them as baseline discriminators or non-discriminators. Each subject then underwent discriminative conditioning consisted of 8 trials of one of the odorants (the CS+) paired with a co-terminating mild wrist-shock and 8 trials of the other odorant (the CS-) presented alone. Odorants were counterbalanced across subjects and trials were presented in random order. Odorant-evoked skin conductance responses were recorded throughout conditioning. Subjects very quickly (within the first few trials) developed a preferential enhancement of the SCR evoked by the CS+ odorant, including the group of non-discriminators that performed poorly on the baseline olfactory assessment. Post-conditioning perceptual testing on a subset of these subjects revealed that these non-discriminators exhibited an impressive improvement in their ability to discriminate the two odorants compared to their own pre-conditioning baselines. Control groups receiving odors without shocks or shocks without odors showed no differential SCR and no improvements in perceptual discrimination. Interestingly, a subset of participants with relatively high levels of trait anxiety (assessed via the State-Trait Anxiety Inventory) exhibited much

less difference in the SCR to the CS+ and CS- after conditioning compared to participants with normal levels of trait anxiety, which is consistent with previous reports. The results of this study highlight the capacity of the olfactory system for rapid plasticity in response to fear learning.

Russo AS, & Parsons RG *Stonybrook*

Acoustic startle response as a predictive index of a PTSD-like phenotype in rats Although a large portion of the population is exposed to a traumatic event at some point, a relatively small percentage of the population develops post-traumatic stress disorder (PTSD). The disparity between the number of individuals who are exposed to trauma and the number of individuals who develop PTSD suggests the presence of susceptibility factors. Despite evidence for the presence of factors that make some individuals more likely to develop PTSD than others, prospective models that aim to identify susceptible populations prior to trauma are limited. Abnormal acoustic startle response (ASR) has been shown to be related to PTSD, implicating this reflex as a potential predictor of the development of PTSD-like symptoms. Because poor extinction learning and retention of extinction learning are characteristic of patients with PTSD, it is of interest to determine if abnormal ASR is predictive of the development of such deficits. To determine if the ASR can be used to predict the development of a PTSD-like phenotype, the relationship between baseline ASR and freezing behavior following fear conditioning was assessed in 45, adult, male Sprague-Dawley rats. Baseline ASR was measured for each rats as the average startle amplitude across 30 trials of a 50 msec, 95 dB white noise burst. Following startle assessment, the rats were exposed to a Pavlovian fear conditioning paradigm consisting of 2 presentations of a 30 sec, 4 kHz, 76 dB tone which co-terminated with a 1.0 mA foot shock. After fear conditioning, the rats received an extinction training session, consisting of 20 presentations of the tone in the absence of the shock, and an extinction testing session, consisting of 8 presentations of the tone in the absence of the shock. Freezing behavior was measured throughout conditioning and testing as an indicator of fear, and was used to calculate "within-session extinction" scores and "extinction retention" scores for each rat. Analysis of the relationships between baseline ASR and our measures of fear revealed that low baseline ASR was associated with poor within-session extinction learning and poor retention of the extinction memory. Furthermore, the rats were ranked based on their baseline ASR, and assigned to either a "low," "medium," or "high" startle group. Although the groups did not differ in retention of the conditioning memory or rate and magnitude of extinction learning, "low" startle rats had significantly poorer retention of extinction learning than "high" startle rats. The results show that low baseline ASR is associated with poor retention of extinction learning following extinction training. Since impaired ability to recall extinction learning is characteristic of patients with PTSD, the results suggest that baseline ASR may have value as a predictive index of the development of a PTSD-like phenotype.

Saddoris MP *U Colorado*

Getting shell-acked: Critical differences in phasic dopamine signaling in the nucleus accumbens subregions during associative learning in normal and cocaine-experienced rats A wealth of studies have consistently demonstrated important roles for dopamine (DA) signaling in the nucleus accumbens (NAc) in associative learning, including aspects like reward prediction error and conditioned approach. However, recent work has suggested that phasic DA release elicited during motivated behaviors can strikingly differ between terminal regions of DA neurons within the NAc, and in this talk, I argue that these distinct patterns of release are linked to different aspects of associative learning. Using a chained instrumental task, we find that DA release in the NAc Core appears to encode information consistent with reward prediction error hypotheses, while DA release in the medial NAc Shell appears to track the significance of all salient stimuli, reminiscent of Incentive Salience models. The functional significance of these signals appears to be critical for supporting normal associative behaviors. In a Pavlovian paradigm, previous experience with repeated cocaine self-administration induces significant alterations in the patterns of phasic DA release to Pavlovian cues in both the core and shell, while animals displaying this impaired DA signaling during first-order conditioning produce abnormal conditioned approach behaviors and a deficit in learning second-order Pavlovian associations. Collectively, these findings suggest that DA supports multiple but related aspects of motivated behavior during Pavlovian learning, and that disruption of these signals by chronic drug abuse may contribute to maladaptations in addicted population that can contribute to persistent drug relapse. *NIDA DA035322*

Sanders HR, & Stanton ME *U Delaware*

Pre-weanling rats can acquire, but not retain contextual associations in object-in-context and contextual fear conditioning paradigms. It is often thought that pre-weanling rats lack the neuronal developmental to encode and retain conjunctive contextual information (Rudy, 1993). Previous studies report that the ontogeny of contextual learning correlates with the development of the hippocampal system (Rudy, 1993; Schiffino et al., 2011). While many report contextual learning parallels hippocampal development, our lab has previously shown differential ontogeny in two different contextual learning paradigms, the context pre-exposure facilitation effect (CPFE, Jablonski et al, 2010), which emerges between Postnatal Day (PD) 17 and 24; and object-in-context recognition (OiC, Ramsaran et al, 2015), which is present on PD17. The current set of experiments were designed to address whether or not PD17 rats' differential performance of contextual learning is due to an encoding or a retention

deficit, by varying the sample to testing intervals of both the CPFE and OiC tasks. Experiment 1 found that PD17 rats were able to perform the OiC task after a short 5-minute sample-to-test interval, but not a long 24-hr sample-to-test interval. Experiment 2 and 3 used the CPFE and found that PD17 rats are able to acquire context-shock associations, and display freezing behavior after short retention intervals but not after 24 hrs. Additionally, it was found that freezing behavior decreases as the sample-to-test interval increases. In summary the current findings suggests that pre-weanling animals are able to acquire context representations, but are unable to retain context-shock or context-object associations for 24-hrs. Thus, during context learning, pre-weanling rats show a consolidation or retrieval deficit as opposed to an encoding deficit. *NIH grant R01 HD075066-01A1 to MES*

Scaplen KM, Bounds HA, Ekins TG, Huynh S, Savory N, & Kaun KR *Brown*

Mapping neural circuits for alcohol reward memories in Drosophila Reward neural circuitry must accurately and flexibly encode the affective outcome of an organismâĂŹs experiences to successfully guide future behavior. Dopamine is central to this process, however, a comprehensive understanding is still lacking. This is partly due to the heterogeneity of neurons involved and the neural contexts within which they are found. The development and refinement of neurogenetic tools make invertebrates, such as the fruit fly, Drosophila melanogaster, an attractive model within which to study reward circuitry with an unprecedented resolution. We use the Drosophila model to study how reward memories for complex stimuli, such as alcohol, are established. Alcohol has both aversive and rewarding properties. However, in both flies and mammals, the enduring memories of an intoxication experience are rewarding. With the availability of sophisticated neurogenetic tools that have precise spatial and temporal control we are investigating how alcohol reward memories persist within a remarkably complex circuit. We found that encoding alcohol memories requires activity of a large population of dopamine neurons, but expressing these memories requires only a subset of these neurons. Further, we identified a glutamatergic feedback loop required for re-activation of this subset of dopamine neurons during memory expression. With an identified dopamine-acetylcholine-glutamate reward microcircuit, it is now possible to investigate how this circuit changes with experience and predicts reward. This work provides valuable insight to the dynamic qualities of memory and how the long lasting reward memories for alcohol intoxication are formed. *Smith Family Award for Excellence in Biomedical Research; Rhode Island Foundation Medical Research Fund 20144133, BIBS Center for Nervous System Function COBRE Project Leader Award 5P20GM103645-03 (NIGMS)*

Schepers ST, & Bouton ME *U Vermont*

Renewal in the Context of Stress: A Potential Mechanism for Stress-induced Reinstatement. Exposure to a stressor can cause the relapse of extinguished drug taking ("stress-induced reinstatement"). Interestingly, behaviors reinforced with food are not normally susceptible to such relapse after stress. One explanation is that drug use may uniquely activate the stress system. Drug seeking is therefore acquired in the context of stress and becomes susceptible to ABA renewal when stress occurs after extinction. A series of experiments tested this hypothesis. In the first, rats received 10 daily sessions in which lever pressing was reinforced with sucrose pellets. Group Acquisition Stress received daily exposure to a stressor from a multivariate stress protocol immediately prior to Sessions 4-10; a control group received no stress. Over the next 5 days, all rats then received daily extinction sessions (lever responses no longer produced sucrose pellets) without prior stress. Over the final two days, lever pressing was tested in a session preceded by a stressor and another session without stress (order counterbalanced). Rats in Group Acquisition Stress responded at a much greater rate in the post-stressor test. There was no such effect in the controls. The results support the notion that stress may function as a context in which behavior is initially learned: Stress exposure after extinction may cause relapse because it returns the organism to the original learning context (ABA renewal). Additional experiments examined a related "incentive learning" explanation which holds that consuming sucrose following stress allows the animal to learn that sucrose "makes it feel good" in the context of stress. *NIH Grant # R01 DA033123*

Schoenbaum G *NIDA*

Artificial dopamine transients are sufficient to unblock model-based learning in a preconditioning task Associative learning is driven by prediction errors. Dopamine transients correlate with these errors, which current interpretations limit to endowing cues with a scalar prediction reflecting the value of future rewards. These reward prediction errors are thought to support only a relatively limited form of learning in which predictive cues are endowed with a scalar quantity that reflects the rewarding value of future events. This so-called cached or model-free value does not capture any specific information about those future events. Yet much mammalian behavior reflects specific information about predicted events, rewarding or otherwise, revealing the existence of a rich associative model of the environment. Can dopamine transients support the formation of such model-based associations, or is their involvement in learning restricted to the formation of model-free associations that contain only information about scalar value? Here, we tested this question. Using a novel experimental design, we show prediction errors underlying sensory preconditioning can be blocked behaviorally and reinstated by optogenetically activating dopamine neurons at the time of the missing prediction error. These results establish that learning of a world

model is also driven by prediction errors, and that, contrary to existing canon, dopamine transients can support this type of learning. Our findings open up new possibilities for how these biological signals might support associative learning in the mammalian brain. *NIDA-IRP*

Shang A, Bylipudi S, & Bieszczad KM *Rutgers*
Epigenetic mechanisms dynamically facilitate learning in an auditory discrimination task Epigenetic mechanisms that modulate gene expression âĂŞ such as histone modification âĂŞ are key for regulating neuroplasticity. Blocking histone deacetylases (HDACs) has been shown to facilitate various forms of memory by releasing the brakes on neuroplasticity (e.g. McQuown et al., 2011; Stefanko et al., 2009). Recent work in the auditory system using a simple single-tone associative learning paradigm suggests that pharmacological inhibition of HDAC3 via RGFP966 enhances memory formation for highly specific sound features and facilitates unusually specific retuning of the primary auditory cortex (A1) to auditory features of learning experiences (Bieszczad et al., 2015). Here, we set out to determine if the HDAC3-mediated increase in specificity of A1 reorganization and memory for sound frequency would facilitate acquisition in tasks that require frequency discrimination. We designed a two-tone frequency-discrimination (2TD) task that required animals (adult male rats) to learn to discriminate between two spectrally-distant frequencies (5.0 vs. 11.5 kHz; both 70 db SPL). Bar-presses to the CS+ tone were rewarded by access to water, while bar-presses to the CS- resulted in an extended inter-trial delay ("time out"). As these sounds are spectrally different, any HDAC3-mediated effect could be attributed to associative memory processes per se rather than purely perceptual processes. The first three sessions of 2TD were followed by post-training injections of the HDAC3 inhibitor, RGFP966 (10 mg/kg; s.c.), or Vehicle. Data show that three days of RGFP966 treatment enabled rats to acquire 2TD more rapidly, reaching asymptotic levels of performance two days before vehicle-treated animals. This supports the hypothesis that A1 is under epigenetic regulation by HDAC3 to enable auditory associations to become better consolidated during incremental associative learning experiences with sound. This prompts a novel investigation into the temporal dynamics of epigenetic regulation that may convert the sensory details of transient experiences into long-term memory by releasing the brakes on sensory cortical representational plasticity, thereby acting as a mechanism to "capture" associative information from experience into memory (Phan & Bieszczad, 2016). *NIDCD/NIH (R03DC014753-01)*

Sharp JL, Miller ME, Fountain SB, & Riccio DC *Kent State*
Adolescent methylphenidate exposure causes sex-specific differences in adult rat serial pattern retention Adolescent exposure to methylphenidate (MPD) impairs serial pattern learning in adult male rats (Rowan et al., 2015). The current experiment examined the effects of adolescent MPD on pattern retention in male and female adult rats. Male (N=12) and female (N=11) rats were given once-daily intraperitoneal injections of 20.0 mg/kg of MPD or saline during adolescence from P21-55. Male and female rats learned a pattern, 123-234-345-456-678-781-818, where digits represent the spatial locations of 8 nose-poke receptacles within an octagonal chamber. The pattern consisted of chunk-boundary, within-chunk, and violation elements, which assess stimulus-response learning, abstract rule learning, and multi-item learning, respectively. Dashes indicate brief pauses that served as phrasing cues. Following the training phases, rats received a 5-week retention period. Then, a retention test determined if adolescent MPD exposure caused a retention deficit. An ANOVA conducted on data from the last day of training found no significant differences for sex or adolescent drug exposure. In contrast, although a 2 (sex) x 2 (drug) ANOVA on retention data did not indicate significant effects ($p > .05$), t-tests comparing MPD and control retention for each sex indicated that MPD-treated males made fewer correct responses on the violation element than saline-injected males, $t(1, 22) = 2.14$, $p = .043$, but no such effect was observed in females. These results indicate that following adolescent exposure to MPD, males, but not females, displayed significantly impaired retention for the violation element of the pattern. The fact that adolescent MPD exposure caused sex-specific impairments in adult serial pattern retention indicates that early exposure to MPD had different effects on male versus female rat brain development. However, it is still to be determined whether this sex-specific effect depends on differences in drug sensitivity, mechanism of action, or a combination of the two.

Sheynin J, Baidya S, & Liberzon I *U Michigan*
Acquisition and generalization of avoidance: A mismatch between expectancy and behavior Excessive avoidance behavior is a predominant symptom in all anxiety disorders and posttraumatic stress disorder (PTSD). While two drivers are commonly implicated in avoidance behavior (fear and cognitive expectancy), the mechanism that results in exaggerated and potentially maladaptive responding is yet undefined. Here, we used a computer-based task with mild aversive events, to specifically focus on the cognitive basis of avoidance behavior. On this task, participants control a spaceship avatar and shoot an enemy spaceship to gain points, as well as learn to hide their spaceship in "safe areas" to prevent (avoid) point loss. Total accumulated points are translated into a monetary reward at the completion of the session. Avoidance response could take place during warning signals that predict an aversive outcome on all, or on only 60% of the trials (deterministic or probabilistic contingency, respectively). Twenty healthy young adults from University of Michigan and surrounding area were recruited and tested on the Spaceship task. Avoidance behavior and self-reports

of expected risk associated with each one of the warning signals were recorded. While participants successfully dissociated the deterministic and probabilistic signals on expectancy scores, they demonstrated a similar avoidance responding during these signals. Interestingly, only during the probabilistic signal, expectancy was correlated with avoidance behavior. In addition, when participants were presented with novel warning signals that share similarities with the previous learned signals, they showed a greater generalization of expectancy than of behavior. Taken together, these findings suggest that while individuals learn the contingency and the potential risk associated with warning signals, their avoidance behavior does not always follow the same pattern. This work emphasizes the need to operationalize avoidance behavior, rather then rely on self-report measures, and paves the way for future work that would investigate other variables that can affect avoidance behavior, e.g., risk and loss aversion. *Departmental funding (Department of Psychiatry) and Undergraduate Research Opportunity Program (UROP), University of Michigan*

Sheynin J, Shind C, Ebanks-Williams Y, Beck KD, & Myers CE *U Michigan*

Greater avoidance behavior in individuals with symptoms of posttraumatic stress disorder (PTSD) Avoidance, an adaptive behavior to cause omission of aversive events, can become pathological if the behavior continues in the absence of threat. Avoidance is a core symptom of posttraumatic stress disorder (PTSD). However, little is known about whether individuals with PTSD show a general cognitive bias to acquire and express avoidance, in situations not related to trauma or fear. Here, we used a computer-based âĂIJspaceshipâĂİ task to examine operant acquisition and extinction of avoidance in 119 participants with severe PTSD symptoms (PTSS) vs. few/no PTSD symptoms (noPTSS). In the task, participants controlled a spaceship and could shoot at on-screen targets to gain points, or hide in âĂIJsafe areasâĂİ to escape from (terminate) on-screen aversive events (spaceship destruction and point loss). The aversive event could be avoided by anticipatory hiding during warning signals that predicted upcoming threat. Most participants learned to escape; however, PTSS participants showed more avoidance across trials, and this was particularly due to more avoidance behavior in PTSS females compared to noPTSS females. Acquisition was followed by an extinction phase in which warning signals no longer predicted upcoming threat. Avoidance behavior decreased across extinction trials; the effects of PTSS and gender approached but fell short of significance. These results show that PTSD symptoms are associated with propensity to acquire and express avoidance behavior, even in a cognitive task that does not explicitly involve trauma or fear, suggesting that— in addition to the common fear-based interpretation of PTSD—a more cognitive approach could enhance understanding and treatment of PTSD. *Supported by Merit Review Award I01 CX000771 from the U. S. Department of Veterans Affairs Clinical Sciences Research and Development Service*

Shiflett MW *Rutgers*

Action Control Deficits in Rodent Models of Psychiatric Disorders Goal-directed behavior allows for flexible, adaptive responses to changing environmental conditions. This ability relies on a network of brain regions that link the cortex with limbic and basal ganglia nuclei. When disease or injury affects this network, inflexible and maladaptive behavior may arise. Examining how goal-directed behavior is modified in psychiatric disorders may shed new light on disease mechanisms and open new avenues to treatment. I will present data from studies examining goal-directed action control in rodent models of attention-deficit/hyperactivity disorder (AD/HD) and Autism Spectrum Disorder (ASD). Using operant tasks, we found evidence for impaired goal-directed action control in Spontaneously Hypertensive Rats, an AD/HD model. Furthermore, methylphenidate, a psychostimulant used to treat AD/HD, was effective in remediating action control deficits in SHR rats. In separate studies, we examined mice deficient in semaphorin signaling, which critically regulates brain development and has been associated with ASD. Loss of semaphorin signaling in mice produced abnormal corticostriatal connectivity, increased stereotyped repetitive behaviors, and led to deficits in goal-directed responding in an operant task. Taken together, these data are consistent with a growing body of evidence from human and animal studies suggesting that disparate psychiatric disorders share common impairments in action control and affect overlapping cortico-basal ganglia circuitry. Assessments of goal-directed action control may serve as a useful endophenotype to unify diagnostic studies of psychiatric disorders.

Shipman ML, Trask S, Bouton ME, & Green JT *U Vermont*

The prelimbic cortex attenuates responding of undertrained but not overtrained actions The role of the prelimbic cortex (PL) has been extensively studied in operant behavior. A typical result is that a lesion to the PL affects behavior that is still goal-directed (i.e., sensitive to reward devaluation) but not habitual behavior (i.e., behavior that is insensitive to reward devaluation). PL lesions will render a typically goal-oriented response insensitive to reward devaluation, but leave an extensively trained habit intact. However, the "habit" demonstrated by PL-lesioned rats typically reflects a general suppression of responding. This accords well with previous findings from our laboratory that demonstrate that PL lesions selectively weaken excitatory context behavior, rather than affecting goal-directed behavior or habitual behavior per se. To further elucidate the role of the PL in expression of goal-directed or habitual behavior, we used a within-subject design to examine both an overtrained and an undertrained operant response. Prior to training, rats received

stereotaxic surgery to implant guide cannulae into their prelimbic cortices. Following recovery, rats learned two operant responses, each of which produced a food reinforcer on a VI 30 schedule, R1 and R2, each in its own context (Context A and B, respectively). R1 received extensive training (24 30-min sessions) and R2 received minimal training (4 sessions). Rats then received lithium chloride injections that were either paired or unpaired with sucrose pellets in both contexts. Devaluation cycles continued until paired rats rejected all pellets. On test day, rats received either an infusion of saline or baclofen/muscimol into their prelimbic cortices and were tested (in extinction) on both their R1 and R2 responses, each in its respective context. Interestingly, no habit was demonstrated in the extensively trained response (i.e., rats were still sensitive to reward devaluation). However, following reward devaluation, rats with an inactivated PL showed a selective decrement in responding on the undertrained response. This may imply that the PL is involved in expression of a particular response-outcome (R-O) pairing early on in learning. However, as a response is overtrained the PL is no longer necessary for expression. Our results show that an overtrained response that is still sensitive to reward devaluation no longer appears to be dependent on the prelimbic cortex while an undertrained action remains dependent. This contributes to our understanding of operant responding as a continuum, rather than either an action or a habit.

Shors TJ, Millon EM, Chang HYM, Olson RL, & Alderman BL *Rutgers*

Do Sex Differences in Rumination Explain Sex Differences in Depression? It is generally accepted that women tend to ruminate more than men do and these thought patterns may be associated with depressive symptoms (Nolen-Hoeksema et al., 1999). Based on these findings, we considered here whether the relationship between rumination and depression is stronger in women than in men and if so, whether this might explain the high incidence of major depressive disorder (MDD) in women and finally, whether the association can be disrupted through a mind/body intervention. A recent study of adult men and women, most of whom were clinically depressed, participated in an intervention known as MAP Training, because it combines "mental" training with meditation and "physical" training with aerobic exercise (Shors et al., 2014). After eight weeks of training, both men and women reported significantly fewer symptoms of depression and fewer ruminative thoughts (Alderman et al., 2016). Statistical correlations between depressive symptoms and ruminative thoughts were strong and significant (r's > 0.50; $p<0.05$) for both men and women before and after MAP Training. However, only in women did depressive symptoms relate to "reflective" ruminations, which involve analyses of past events, feelings and behaviors. This is also the only relationship that dissipated after the intervention. In general, these analyses suggest that the strength of the relationship between depressive symptoms and rumination does not necessarily explain sex differences in depression; but because the relationship is strong, targeting rumination through intervention can reduce the incidence of MDD in humans, most of whom are women.

Sinha N, Mattfeld AT, & Gluck MA *Rutgers*

Dopamergic modulation of reward learning across the lifespan Prior research by our lab has shown that unique subregions of the striatum differentially participate in the learning of associations through reward and punishment. This dissociation is thought to reflect modulation in the neural activity by dopaminergic neurons—consistent with studies showing that striatal asymmetries in dopamine receptor binding predict individual differences in motivational bias. In the current study, we explored how the monotonic depletion of dopamine across the lifespan, modulates individual differences in reward and punishment based learning, and their corresponding neural correlates. In comparing older adults to younger adults, we found that while there were no between-group differences in punishment learning, older adults showed reward learning deficits. Further, these deficits correspond with hyperactivity in the ventral striatum. Taken together these results are consistent with both the dopamine hypothesis of aging, as well results from non-medicated PD patients.

Sullivan RM, Opendak M, & Wilson D *Nathan Kline Institute - NYU*

Learned maternal cues modify sensory processing and learning The infant must learn about the mother during the attachment process. Once the maternal cues are learned, these cues take on unique ability to modulate the infantâĂŹs immediate neurobehavioral responses. Here we show maternal control of the infant rat brain and behavior in two different situations: 1) during social buffering of pain and the supporting neurobiology (fos) and 2) during ongoing mother-infant interactions within the nest using telemetry LFP. Results show that maternal control of the infant brain involves at least 2 mechanisms: 1) attenuation of pupsâĂŹ stress response which causes changes in amygdala, dopamine and HPA neural activity and 2) alteration of neural oscillations and functional connectivity between brain regions. Using a Scarcity Model of maternal abuse, we show that the ability of maternal cues to influence pup neural and behavioral response is diminished. These results suggest that critical features of the caregiver are learned and once learned take on powerful control of the infantâĂŹs processing of sensory information and brain activity. This learning is influenced by the quality of care received by the infant.

Tallot L, Diaz-Mataix L, Graupner M, & Doyère V *CNRS*

Interactions in an amygdalo-prefronto-striatal circuit for processing the CS-US interval In Pavlovian aversive con-

ditioning, the subject not only learns an association between a neutral conditioned stimulus (CS) and an aversive unconditioned stimulus (US), but also that the CS predicts the time of arrival of the US. Learning of the association and the temporal relationship between both stimuli requires minimum training (Davis et al, 1989; Diaz-Mataix et al, 2013). The prefrontal cortex (PFC) and the striatum (STR) are believed to play a role in interval timing (Buhusi & Meck, 2005), whereas the amygdala is essential for learning the CS-US association and may have a role in CS-US interval processing as well (Diaz-Mataix et al, 2014). In search of neural correlates of temporal and associative processing early in learning, we recorded local field potentials (LFPs) simultaneously in the basolateral part of the amygdala (BLA), the prelimbic part of the medial prefrontal cortex (mPFC) and the dorsomedial part of the striatum (dmSTR) that form an interconnected network, during a long-term retention test 24h after a single training session. Conditioning consisted of 10 trials with a 60-sec tone CS paired with a footshock US arriving either 10 or 30 seconds after the CS onset, a paradigm that induces reliable learning of the CS-US interval (Diaz-Mataix et al 2013). Interestingly, the comparison of the rats trained using a 30 sec interval with those trained using a 10 sec interval showed a temporal modulation of freezing that followed the scalar property of time (i.e. higher variability for longer durations). The time-frequency analysis of the LFPs highlighted an increase in theta (4-7 Hz) power in the mPFC and the dmSTR and a decrease in beta (13-17 Hz) in all three structures. Moreover, these patterns were modified depending on the CS-US duration learned, with a return to baseline after the expected time of US arrival. Coherence (i.e., the synchronization of oscillations between brain structures) was also modulated differentially depending on the duration learned during aversive conditioning between mPFC and dmSTR, as well as between BLA and dmSTR. These results suggest that the three structures (BLA, mPFC and dmSTR) compute the CS-US interval in a simple Pavlovian associative task. More importantly, the results suggest that these structures form a functional network processing the temporal expectancy of an aversive event. *LIA LearnEmoTime CNRS, PUF Emotion & Time, ANR*

Thrailkill EA, Rojas G, & Bouton ME *U Vermont*
How to Break a Habit Habits are behaviors that are insensitive to the value of their consequences. Recent computational theories suggest that habits are composed of several actions executed rapidly as a single unit. On this view, the organism selects a habit instead of a deliberate action when the reward rate for rapid performance is high. This suggests that habits will become actions (i.e., deliberative) when the reward rate is decreased or discontinued. In the present study, rats pressed a lever for a reinforcer (R-O1) over an extended period of training that created a habit. For half the rats, the reinforcer was then devalued by pairing it with illness. The remaining rats received the reinforcer and illness unpaired. Half the rats from each group then received an extended session in which lever pressing was extinguished. Responding decreased and reached essentially zero during the test; however, responding did not become sensitive to devaluation, suggesting it remained a habit throughout the test. The remaining rats were tested with lever pressing for a different reinforcer (O2). Here, O2 caused responding in the paired group to decrease robustly (compared to the unpaired group); O2 thus caused the behavior to convert to an action. Responding decreased even though the rats consumed every O2 pellet, and showed no generalization of the taste aversion from O1 to O2. Therefore, changing the outcome converted a habit back into an action, but extinction training did not. The results suggest a method for breaking a habit, but do not support the computational account of habits.

Trask S, & Bouton ME *U Vermont*
Reducing the negative impact of context change on an operant response A context switch following training weakens an operant response. One way to reduce this decrement is to train the response in multiple contexts. On one view, this causes conditioning of more stimulus elements that are common across contexts, increasing generalization. On another view, training procedures that make memory retrieval difficult (like inserting context changes) increase memory strength (Bjork & Bjork, 1992). Two experiments separated these hypotheses. In Experiment 1, rats learned to nosepoke for a food reinforcer. For one group, all six acquisition sessions occurred in Context A. For a second group, two sessions occurred in Context A, two in Context B, and two in Context C. Rats were then tested in the most recent context and in a novel context. Both groups showed a response decrement in the novel context, but it was less pronounced in the variably-trained group. Experiment 2 asked whether long retention intervals, which also make retrieval difficult, likewise reduce the context change effect. All acquisition sessions occurred in the same context. For one group, every two sessions were separated by a 14-day retention interval. For another, all sessions were separated by the usual 24 hrs. Responding was then tested in the acquisition context and a novel context. Despite the retention interval disrupting acquisition performance like context change did in Experiment 1, the final context switch affected performance similarly in the two groups. The results suggest that conditioning of common elements, rather than difficult retrieval practice, creates a behavior that is more resistant to decrement caused by context change. *RO1 DA 033123*

Travaglia A, Bisaz R, Sweet ES, Blitzer RD, & Alberini CM *NYU*
Latent infantile memories and critical period mechanisms Episodic memories formed during infancy seem to be forgotten, a phenomenon known as infantile amnesia. Infantile amnesia is conserved throughout evolution, as it has been

described in humans as well as in rodents. In spite of this apparent memory loss, early life experiences influence brain development and predispose to psychopathologies, raising the question of which mechanisms underlie infantile memory formation. Using the contextual fear-based task inhibitory avoidance (IA) in infant rats, we found that early life experiences are not lost but stored as latent memory traces for a long time: later reminders reinstate a robust and long-lasting memory. The formation of the latent infantile memory requires the hippocampus and employs mechanisms typical of developmental critical periods, including a BDNF- and mGluR5-dependent expression switch of NMDA receptor subunits from 2B to 2A. Moreover, BDNF administration or mGlur5 activation rescues the infantile amnesia. We suggest that the hippocampus, like sensory systems, undergoes a developmental critical period to become functionally competent. R01-MH074736 and Agalma Foundation

Tricomi E *Rutgers*
Striatal influences on the motivational control of human behavior Rewards and punishments provide information that guide learning and motivate goal-directed behavior. With extensive experience, however, behavior is motivated less by goals and more by antecedent cues that have become associated with a particular action. In this talk, I will discuss my research on how goals and experience influence activation of the human striatum, a key region involved in reward processing and associative learning. I have found using fMRI that the head of the caudate nucleus, a region which lies within the dorsal striatum, is robustly activated in response to rewards earned by performance of goal-directed actions. To investigate the motivational control of behavior as learning progresses, we used a free-operant paradigm and a selective satiety procedure inspired by rodent research on habit learning, and found that with experience, human behavior becomes independent of its consequences, the hallmark of a habit. Meanwhile, striatal activity shifts toward increasing cue sensitivity in the posterior putamen as behavior shifts toward being driven by a habitual response to a cue. Although the use of paradigms similar to those used in animal research aids the translational effort, there is also value in studying pre-existing habits that humans have built up with extensive experience outside the laboratory. Toward that aim, we have recently developed a Go/No-Go task that capitalizes on well-learned associations, such as the âĂIJred light-stopâĂİ and âĂIJgreen light-goâĂİ contingencies. We have found that reversal of familiar contingencies, so that the correct response to a green light is to withhold a response, leads to more errors of commission compared to the reversal of novel color-action contingencies. These findings support the notion that familiar contingencies have become outcome-insensitive habits, and allow us to improve on traditional practices employed in studying behavioral control by providing a new task to study well-learned habits in healthy and clinical human populations. Overall, this research suggests a shift in motivational control of behavior in humans parallel to that found in animals, from goal-directed behavior that elicits outcome-related signals in the head of the caudate, to outcome-insensitive habitual behavior, driven by antecedent cues and corresponding activity in the posterior putamen.

Tumolo JM, Kutlu MG, & Gould TJ *Penn State*
Chronic nicotine alters spontaneous recovery of contextual fear differentially in male and female mice Post-traumatic stress disorder (PTSD) is a devastating disorder with symptoms such as flashbacks, hyperarousal, and avoidance of reminders of the event. Exposure therapy is the most widely-used treatment for PTSD and attempts to extinguish fear responses but relapse following successful exposure therapy is a common problem. In rodents, spontaneous recovery (SR), where extinguished fear responses resurface following extinction, is used as a model of fear relapse. Previous studies from our lab showed that chronic nicotine impaired fear extinction and acute nicotine enhanced spontaneous recovery of contextual fear in adult male mice. In addition, we showed that acute nicotineâĂŹs effects were specific to spontaneous recovery as acute nicotine did not affect recall of contextual fear conditioning in the absence of extinction. However, effects of chronic nicotine administration on spontaneous recovery are not known. Therefore, in the present study, we investigated if chronic nicotine administration altered spontaneous recovery or recall of contextual fear in adult male and female C57BL6/J mice. Spontaneous recovery subjects were trained and tested in contextual fear conditioning, given five extinction sessions, and were either implanted with mini-osmotic pumps containing 12.6 mg/kg nicotine or underwent sham surgery the day after the final extinction session. Recall subjects were also trained and tested in contextual fear, did not undergo extinction, and were either implanted with mini-osmotic pumps or given sham surgeries on the same day as the spontaneous recovery groups. One week following the surgery, subjects were tested for spontaneous recovery and recall. Our results showed that chronic nicotine significantly enhanced spontaneous recovery in female mice and significantly decreased spontaneous recovery in males. Chronic nicotine had no effect on recall of contextual fear in males or females. Female sham mice also had significantly less baseline spontaneous recovery than male sham mice. Overall, these results show that chronic nicotine administration has a differential effect on spontaneous recovery of contextual fear depending on sex, that female mice are less likely to experience spontaneous recovery without the drug, and that nicotine has no effect on recall of contextual fear. For individuals with PTSD that were successfully treated with exposure therapy, this indicates that women who use nicotine products could have an increased chance of relapse whereas men who use such products may be at a decreased risk. Women who do not use nicotine may also be at a decreased risk for re-

lapse compared to men who do not use nicotine. However, further clinical studies would be necessary to corroborate our results. *This research was funded with grant support from the National Institute on Drug Abuse (T.J.G., DA017949) and Temple University's Creative Arts, Research and Scholarship Grant.*

Voulo ME, & Parsons RG *Stonybrook*
Response-specific sex difference in the retention of fear extinction Not all individuals who experience trauma during their lifetime will develop PTSD. One of the greatest risk factors for developing this disorder is being female, with the lifetime prevalence rate twice as high for women as it is for men. Fear conditioning studies in rodents allow us to study fear extinction learning and retention impairments which may underlie vulnerability factors for PTSD. However, it has been estimated that less than 2% of fear conditioning studies in rodents have been conducted in females, leaving a gap in our knowledge of sex-based differences in fear learning. Our study assessed fear conditioning and extinction learning and retention in male and female rats using two fear conditioning protocols—fear-potentiated startle and freezing to an auditory cue. When measuring freezing behavior, males and females showed similar levels of fear conditioning as evidenced by similar levels of freezing behavior to the auditory cue at the beginning of extinction training. Interestingly, there was a trend towards enhanced within session extinction in females compared to males such that female rats showed less freezing behavior near the end of extinction training. However, when measuring retention of the extinction memory the following day, males and females showed equivalent levels of freezing behavior. Next, we tested fear conditioning and extinction using a fear-potentiated startle procedure. Both males and females showed similar levels of fear-potentiated startle during testing prior to extinction training. However, testing after extinction showed that females exhibited significantly more fear-potentiated startle compared to males, indicating an impairment in retention of the extinction memory for females. Together, the results of the two experiments suggest that impairments in extinction retention similar to what we see in PTSD may emerge for females when measuring startle behavior rather than freezing behavior. *Stony Brook University*

Whitlow, JW *Rutgers*
Nature of the Outcomes and Configural Learning Patterning and biconditional discriminations have been good test-beds for comparing elemental to configural accounts of complex discrimination learning. Theoretical predictions about the relative difficulty of these discriminations depend on whether reinforced and non-reinforced outcomes are treated as cases of reinforcement and lack of reinforcement (with asymptotes of lambda and 0, respectively) or as cases of reinforcement with one outcome for some displays and reinforcement with a different outcome for other displays (with asymptotes of lambda and - lambda). These predictions were tested in comparisons between patterning and biconditional discriminations learning by human participants.

Woon E, Urbanczyk P, Pollock M, Ng K, & Sangha S *Purdue*
Prior trauma impairs safety-fear-reward cue discrimination Up to 20% of individuals exposed to a trauma go on to develop Post-Traumatic Stress Disorder (PTSD). Individuals with PTSD are impaired in dampening their fear response in the presence of a safety cue (Jovanovic et al, 2012), and show blunted responses to reward (Kalebasi et al, 2015). Thus, expression of safety, fear and reward behaviors are altered in PTSD. We aimed to explicitly test the effect of trauma on safety-fear-reward cue discrimination to gain a better understanding of how stress influences future learning of safety, fear and reward cues. This will lead to more effective intervention strategies for PTSD individuals faced with subsequent stressors. In order to test the hypothesis that prior trauma will impair safety-fear-reward cue discrimination, Long Evans rats were trained to discriminate among a) a fear cue paired with a 0.45mA footshock, b) a safety cue in the presence of the fear cue resulting in no footshock, and c) a reward cue paired with sucrose delivery. Animals exposed to acute trauma experienced 15 unsignaled 1.0mA footshocks in context A 9 days prior to safety-fear-reward cue discrimination training (context B). Control animals were exposed to context A without footshocks. Preliminary data indicate that animals exposed to the acute trauma failed to show a significant reduction in freezing in response to a safety cue that is presented during the fear cue. In contrast, non-trauma controls did show a significant reduction in freezing during combined fear and safety cue presentation. Concurrently, animals exposed to prior trauma showed a significant reduction in reward seeking behavior in response to the reward cue compared to non-trauma controls. Together, these data indicate that prior trauma 1) impairs the ability to discriminate between danger and safety cues and 2) decreases reward seeking.

Ye X, Kapeller-Libermann D, Travaglia A, & Alberini CM *NYU*
Prefrontal circuit and synaptic mechanisms underlying retrieval-mediated fear memory enhancement and extinction suppression Maladaptive modulations of memory strength and flexibility are commonly observed in many neuropsychiatric disorders, such as anxiety, depression, and post-traumatic stress disorder. Understanding the neural circuit and mechanisms modulating memory strength and flexibility is crucial for developing effective treatments for these disorders. Modulation of fear memory occurs naturally with memory retrieval. Brief re-exposure to the context in which a threat was recently experienced leads to strengthening of the fear memory, whereas re-exposure to the context for prolonged period or at a remote time point favors extinc-

tion, which decreases the conditioned response. These opposite behavioral outcomes raise the following questions: how does memory fear strengthening vs. extinction occur? Are the mechanisms that strengthen or extinguish the memory mutually exclusive? Or do they crosstalk, thus regulating the final outcome? We explored these questions with the inhibitory avoidance (IA) task in rats. First, using Designer Receptors Exclusively Activated by Designer Drugs (DREADD), we have found that direct dorsal hippocampal (dHC) input to the prelimbic cortex (PL), a subregion of the medial prefrontal cortex, is necessary for retrieval-mediated memory enhancement, but not for extinction, which, in contrast, requires a direct input from dHC to the infra limbic (IL) subregion. Second, in the PL, IA training increased the levels of cell adhesion molecules specific for excitatory and inhibitory synapses, neuroligin 1 (NLGN1) and neuroligin 2 (NLGN2), respectively, through brain-derived neurotropic factor (BDNF)-dependent mechanisms. Blocking PL NLGN1 prevented retrieval-mediated memory strengthening, but did not block extinction. In contrast, blocking PL NLGN2 facilitated extinction through increase of IL activity. Collectively, these findings suggest that retrieval-mediated memory enhancement and extinction use distinct neural circuits and mechanisms. Brief recent memory retrieval strengthens memory through recruiting direct dHC to PL projections as well as excitatory and inhibitory synaptic changes in the PL, which coordinate fear memory strengthening and suppression of extinction. *This study is supported by NIMH R01 MH074736 to C.M.A and NARSAD Young Investigator Grant to X.Y.*

Zanca RM[1,3], Caamano-Tubio R[2], Avila JA[1,3], Serrano PA[1,3], & Delamater AR[2,3] [1]*Hunter College - CUNY;* [2]*Brooklyn College - CUNY;* [3]*Graduate Center of CUNY*

The Role of GluA1 and GluA3 trafficking during Pavlovian Reward Conditioning and Extinction Pavlovian Conditioning (PC) is a behavioral model for learning that occurs through associations. Appetitive PC is a model used to investigate appetitive-reward based learning. Very little is known about what molecular mechanisms in the brain underlie Appetitive PC and extinction. Previous work has revealed that the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr) subunit GluA1 is preferentially trafficked in the hippocampus shortly after spatial-memory acquisition. Furthermore, AMPAr subunit GluA3 is preferentially trafficked in the lateral amygdala during fear-memory consolidation. Thus, we hypothesized that Appetitive PC could also mediate differential AMPAr subunit trafficking in the Basolateral Amygdala (BLA) and other brain regions. The present study analyzed expression of molecular markers via western blotting in the BLA, Nucleus Accumbens (NAc) and Dorsal Striatum (DS), 3 brain regions that play pivotal roles in PC. The markers that were analyzed include: AMPA receptor subunits GluA1 GluA2, GluA3; Protein Kinase C iota/lambda (PKCι/λ) and atypical Protein Kinase M zeta (PKMζ). Analyzing these markers can reveal synaptic plasticity changes that occur as a result of Appetitive PC. Rats were trained on a Pavlovian magazine approach-conditioning task in which a short duration auditory stimulus (15 s, 1500 Hz tone) was paired with delivery of a food pellet. Following 8 sessions of conditioning, rats either underwent 5 days of extinction training in which the tone CS occurred without food reward (Extinction), or were exposed to the experimental context without any scheduled events (No-Extinction). On the following day, rats were given 4 non-reinforced test trials with the tone CS and then sacrificed 2 hours later. A third group of rats (Random) were trained on a truly random control contingency procedure in which an equal number of tone CS and food pellet US presentations occurred in each acquisition session; however, these two events occurred randomly in time. For the test-phase of the study, Random subjects were exposed to the experimental context without any events and were tested like the other two groups on the final day. The results from this study showed clear behavioral differences in the test day with the No-Extinction group displaying more conditioned magazine approach responses to the tone CS than either of the other two groups. Western blots revealed that in the BLA and NAc, GluA1 is elevated in the Extinction group only. GluA3 and PKCι/λ are elevated in our No-Extinction group in the BLA and DS. GluA2 was elevated in both No-Extinction and Extinction groups in the BLA and NAc. Our current data reveal that appetitive Appetitive Pavlovian conditioning mediates the differential trafficking of AMPAr subunits in different parts of the brain, suggesting that plasticity in these regions could be pivotal to Appetitive PC learning and extinction.

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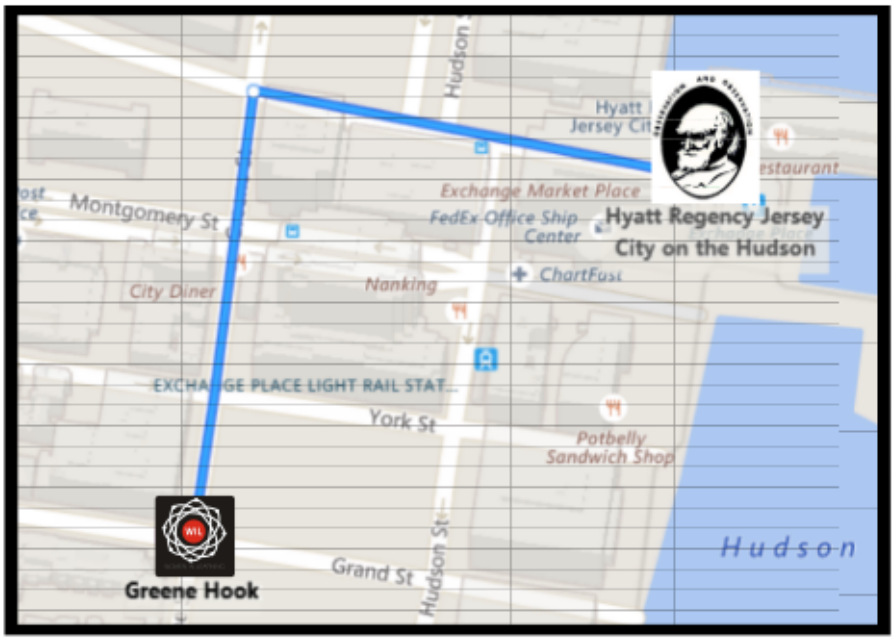
6th Annual Luncheon:

Greene Hooke, Jersey City, NJ
Saturday, October 1
12:15 - 1:30 p.m.
Special Guest: Dr. Regina Sullivan



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