# Pavlovian Society
# Annual Meeting, 2018
# Graduate Iowa City

October 4–7, 2018
Iowa City, IA

**Overview**

| | | |
|---|---|---|
| Thur | 6:00–10:00 PM | Opening Reception<br>Wayne Ballroom A/B<br>Hors d'Oeuvres & Cash Bar |
| Fri | 7:30–8:25 | Breakfast |
| | 8:25–12:20 | Morning Sessions |
| | 12:20–1:50 | Lunch<br>(Exec Committee Meeting) |
| | 1:50–5:30 | Afternoon Sessions |
| | 5:30–7:30 | Posters & Cash Bar |
| Sat | 7:30–8:25 | Breakfast |
| | 8:25–12:00 | Morning Sessions |
| | 12:00–2:00 | Lunch<br>(WIL Luncheon) |
| | 2:00–5:30 | Afternoon Sessions |
| | 5:30–7:30 | Posters & Cash Bar |
| | 7:30–9:00 | Banquet |

**Program**

**Friday (October 5)**

7:30–8:25 **Breakfast**
Outside of Wayne Ballroom A/B

All talks in Wayne Ballroom A/B

8:25–8:30 **John Freeman, PhD** (University of Iowa) Welcome

8:30–9:00 **Mark Stanton, PhD** (University of Delaware) Past President Lecture: Mechanisms of context conditioning in the developing rat

**The Society thanks Iowa Neuroscience Institute; Dept. of Psychological and Brain Sciences, U. Iowa; Plexon; & Elsevier for generous contribution in support of the meeting.**

9:00–10:30 **Symposium: Behavioral advances in animal memory (Leyre Castro, PhD, Chair)**
* **Leyre Castro, PhD and Edward Wasserman, PhD** (University of Iowa) Memory demands and cognitive flexibility in pigeons
* **Jonathon D. Crystal, PhD** (Indiana University) Animal models of episodic memory
* **Danielle Panoz-Brown and Jonathon D. Crystal, PhD** (Indiana University) Replay of episodic memories in the rat
* **Ralph R. Miller, PhD and Cody W. Polack, PhD** (Binghamton University) TOTAL PREDICTIVE Error-Reduction Drives ACQUISITION of Associative Memories: No, No, and No

10:30–10:50 **Coffee Break**

10:50–12:20 **Symposium: Adjusting to a changing world: Individual differences and situation-dependent behaviors in rats and other beasts (Marie Monfils, PhD, Chair)**
* **Nadia Chaudhri, PhD** (Concordia University) Context as a critical cue for alcohol: Striatal and amygdala mechanisms
* **Rebecca Shansky, PhD** (Northeastern University) Tipping the scales: Situational modulators of active vs. passive conditioned fear responses
* **Catherine Hartley, PhD** (New York University) Control and the calibration of motivated behavior
* **Marie Monfils, PhD** (University of Texas, Austin) Heterogeneity of extinction phenotypes in rats

12:20–1:50 **Lunch (on your own)**
Executive Committee Meeting (O'Connor Board Room)

1:50–3:30 **Invited Talks**
* **Ted Abel, PhD** (University of Iowa) Epigenetic mechanisms of memory storage

* **Amy Griffin, PhD** (University of Delaware) Hippocampal-thalamic-prefrontal circuit contributions to spatial working memory
* **Kate Wassum, PhD** (UCLA) Cortical-amygdala circuitry in reward learning & pursuit
* **Rebecca Burwell, PhD** (Brown University) The neural circuitry of spatial context: Beyond the hippocampus
* **Ryan LaLumiere, PhD** (University of Iowa) Amygdala influences on memory consolidation: Insights from multiple memory systems

3:30–3:50 **Coffee Break**

3:50–5:30 **Invited Talks**
* **Krystal Parker, PhD** (University of Iowa) Cerebellar circuits, timing, and cognition
* **Richard Servatius, PhD** (VA Medical Center, Syracuse) Enhanced Eyeblink Conditioning in Active Duty Military and Veterans Expressing PTSD Symptoms. Cerebellar Collusion?
* **Shane Heiney, PhD** (University of Iowa) Predictive control of a motor synergy by the cerebellum
* **Michael Mauk, PhD** (University of Texas, Austin) When output is input: Some consequences of recurrent connections on learning
* **Jennifer Raymond, PhD** (Stanford University) TBA

5:30–7:30 **Posters and Cash Bar**
Benson Room

**Saturday (Oct 6)**

7:30–8:25 **Breakfast**
Outside of Wayne Ballroom C/D

8:25–8:30 **John Freeman, PhD** (University of Iowa) Welcome

8:30–10:00 **Symposium: Beyond "better or worse": Sex differences in learning and memory (Natalie Tronson, Chair)**
* **Shunya Yagi, MSc** (University of British Columbia) Sex and strategy differences in immediate early gene activation and neurogenesis in the hippocampus after pattern separation

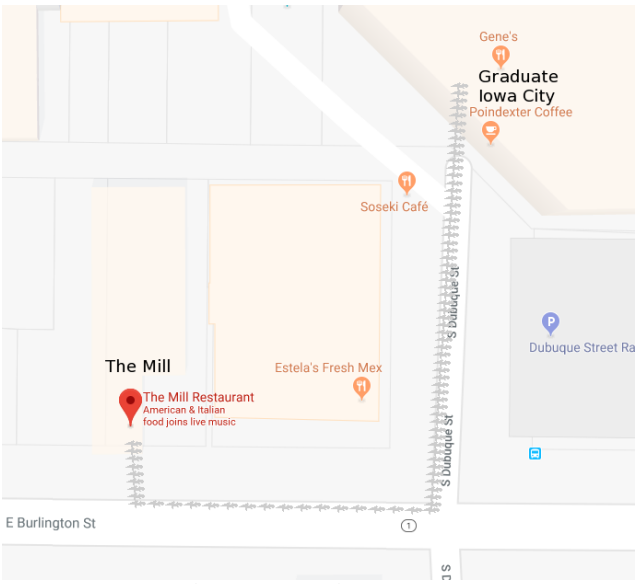


*Figure 1.* Map to the WIL Luncheon

* **Nicola Grissom, PhD** (University of Minnesota) Maximally divergent sex-specific strategies in decision making lead to more optimal performance in females
* **Holly C. Hunsberger, PhD** (Columbia University) Anxiety predicts cognitive decline in a sex-specific manner in Alzheimer's disease mice
* **Natalie C. Tronson, PhD** (University of Michigan) Learning strategies and memory mechanisms: What are females doing?

10:00–10:40 **Women in Learning Talk**
* **Barbara Knowlton, PhD** (UCLA) Reduced sensitivity to devaluation after early-life stress

10:40–11:00 **Coffee Break**

11:00–12:00 **Keynote Address**
* **Edward Wasserman, PhD** (University of Iowa) Precrastination, anticipation, and signalization: Implications for adaptive action

12:00–2:00 **Lunch / Women in Learning satellite meeting**
The Mill (See map)

2:00–3:30 **Symposium: Mind the gap: Neurobiological mechanisms of trace conditioning (Brian Wiltgen, PhD, Chair)**

* **Brian Wiltgen, PhD** (University of California, Davis) How does the hippocampus learn about discontiguous events?
* **Takashi Kitamura, PhD** (University of Texas Southwestern) Role of dopamine D1 receptors in the medial entorhinal cortex on trace fear conditioning
* **Matt Lattal, PhD** (Oregon Health & Sciences University) Epigenetic modulation of deficits in trace fear conditioning following withdrawal from chronic cocaine
* **Craig Weiss, PhD** (Northwestern University) Basic and translational analyses of trace eyeblink conditioning in rabbits and mice

3:30–3:50 **Coffee Break**

3:50–5:30 **Invited Talks**
* **Sheena Josselyn, PhD** (University of Toronto) Making Memories
* **Denise Cai, PhD** (Mount Sinai University) Linking memories across time
* **Jelena Radulovic, PhD** (Northwestern University) Processing memories in the hippocampal-retrosplenial cortical circuit
* **Steve Maren, PhD** (Texas A & M University) The way forward is backward: BNST mediates fear to ambiguous threats
* **Christine Rabinak, PhD** (Wayne State University) Cannabinoid facilitation of fear extinction in patients with posttraumatic stress disorder: A potential therapeutic target

5:30–7:30 **Posters and Cash Bar**
Benson Room

7:30–9:00 **Banquet**
Wayne C/D
Speaker: **Mark Blumberg** (University of Iowa) Freaks for geeks
Awards

## Posters

Generally alphabetical by author except for some moved between days.

***These posters will be presented at Friday's Poster Session.***

1. **Agee LA, Monfils MH**, *(UT Austin)*. Effect of Demonstrator Reliability and Recency of Last Demonstration on Acquisition of a Socially Transmitted Food Preference

2. **Allen, MT, Myers, CE, & Servatius, RJ**, *(Univ. of Northern Colorado; Stress and Motivated Behavior Institute;Dept. of Veterans Affairs )*. Schedules of partial reinforcement with us alone trials do not disrupt classical eyeblink conditioning: empirical and computational findings

3. **Abbott PW, Heskje J, Walsh K, Wu S, Hardie J, Freeman J, Bassuk AG, Parker KL**, *(University of Iowa)*. Cerebellar abnormalities and changes in eyelid conditioned responses in the prickle2 mouse model of autism-like behavior

4. **Bral SR, Farley SJ, Freeman JH**, *(The University of Iowa)*. Amygdala central nucleus inactivation impairs acquisition and retention of delay eyeblink conditioning in female rats

5. **Kim J, Broschard MB, Castro L, Wasserman EA, Freeman JH**, *(Dept of Psychological Brain Sciences, UIowa)*. Roles of medial prefrontal cortex in rodent visual categorization

6. **Broschard MB, Kim J, Love BC, Wasserman EA, Freeman JH**, *(Dept of Psychological Brain Sciences, UIowa)*. Rule-Based and Information Integration Category Learning in Rats

7. **De Corte BJ, Matell MS**, *(University of Iowa, Iowa Neuroscience Institute; Villanova University, Department of Psychology)*. The times they are a changin': Temporal covariance and the common cause hypothesis

8. **Gironda SC, De Corte BJ, Matell MS**, *(Villanova Universisity Department of Psychological and Brain Sciences, Iowa Neuroscience Institute)*. Relational Encoding of Time across Modalities in the Peak Procedure

9. **de Solis CA, Gonzalez Cuauhtémoc U, Galdamez MA, Samuel W. Woodard SW, Carlos E. Salinas CE, Joel N. Miller JN, Hajira Elahl H, Pineda OH, Perish JM, Oad S, Gatica de las Fuentes S, Owen MS, Sandoval Jr. A, Holehonnur R, Ploski JE**, *(The University of Texas at Dallas, Columbia University )*. Overexpression of GluN2B(E1479Q) Within The Basal and Lateral Amygdala Enables The Modification of Strong Reconsolidation Resistant Fear Memories

10. **Dulka BN, Bagetalas ED, Bress, KS, Cooper, MA**, *(University of Tennessee)*. Chemogenetic Activation of an Infralimbic Cortex to Basolateral Amygdala Neural Projection is Sufficient for Resistance to Conditioned Defeat

11. **Escobedo A, Sowinski EM, Herakovich R, Sangha S**, *(Purdue University - Department of Psychological Sciences, Purdue Institute for Integrative Neuroscience)*. The effect of the partial NMDAR agonist D-Cycloserine on conditioned inhibition of fear

12. **Farley SJ, Freeman JH**, *(The University of Iowa)*. Amygdala central nucleus inactivation impairs learning-related spike activity and local field potentials in the basilar pontine nucleus

13. **Ferrara NC, Trask S, Cullen PK, Pullins, SE, Helmstetter FJ**, *(Department of Psychology, University of Wisconsin-Milwaukee)*. Inhibition of thalamic terminals in the amygdala may facilitate extinction learning

14. **Trask, S, Ferrara, NC, Helmstetter, FJ**, *(University of Wisconsin - Milwaukee)*. Optogenetic silencing of the thalamo-amygdala pathway, but not lateral amygdala, results in a long-term decrease in fear expression

15. **Ferri SL, Lee JY, Dow H, Brodkin ES, Abel T** , *(University of Iowa, University of Pennsylvania)*. Fear conditioning deficits in the Pcdh10 mouse model relevant to autism

16. **Fisher H, Pajser A, Fox S, Long C, Gilbert S, Pickens CL**, *(Kansas State University )*. Inactivation of the basolateral amygdala or mediodorsal thalamus but not orbitofrontal cortex during training impairs performance on a multiple-response/multiple-reinforcer operant devaluation task in rats.

17. **Ghobbeh A, Taugher RJ, Alam S, Fan R, Lalumiere RT, Wemmie J**, *(University of Iowa, Department of Psychiatry)*. A novel role for acid-sensing ion channel (ASIC1A) in Pavlovian reward conditioning

18. **Grissom NM, McKee SE, Schoch H, Walsh L, Nickl-Jockschat T, Reyes TM, Abel T**, *(University of Iowa)*. Deficits in learning are common across multiple mouse models of autism

19. **Halverson HE, Mauk MD**, *(Center for Learning and Memory and Department of Neuroscience, University of Texas, Austin, Texas 78712)*. Extinction and reacquisition of conditioned eyelid responses are controlled by eyelid Purkinje cells

20. **Herbst MR, Anochili V, Theodore BB, Gilmartin MR**, *(Marquette University)*. Cued fear discrimination in the stress-enhanced fear learning model of post-traumatic stress disorder.

21. **Heroux NA, Miller LA, Horgan CJ, Rosen JB, Stanton ME**, *(Department of Psychological and Brain Sciences, University of Delaware)*. Inactivation of the medial prefrontal cortex disrupts immediate early gene expression in the ventral midline thalamus and ventral hippocampus during context memory formation

22. **Heskje JP, Halverson HE, Jyotis AK, Williams RM, Parker KL**, *(Iowa Neuroscience Institute, Department of Psychiatry, University of Iowa)*. Pharmacological manipulation of the rat cerebellar cortex at crus I disrupts performance in an interval timing task

23. **Heslin KH, De Corte BJ, Parker KL**, *(University of Iowa )*. Dissociating effects of pharmacological manipulation in the lateral cerebellar nuclei: interval timing or cue discrimination deficit?

24. **Hilz EN, Smith RW, Monfils MH, Lee HJ**, *(The University of Texas at Austin)*. Mapping the estrous cycle to context-specific extinction memory

25. **Hoffman AN, Hsieh E, Pennington ZT, Watson S, Hovda DA, Giza CC, Fanselow MS**, *(UCLA Neurosurgery; Brain Injury Research Center; UCLA Psychology; UCLA Steve Tisch BrainSPORT Program; UCLA Medical and Molecular Pharmacology; Mattel Children's Hospital UCLA; UCLA Psychiatry & Biobehavioral Sciences; Staglin Center for Brain and Behavioral Health)*. Projection specific mechanisms of auditory sensitivity that contribute to enhanced fear after TBI

26. **Rajbhandari AK, Octeau JC, Malvaez M, Chavez J, Nguyen L, Keces N, Waschek JA, Khakh BS, Fanselow MS**, *(University of California-Los Angeles)*. Role of PACAP neuropeptide and PAC1 receptor system in the basomedial amygdala and intercalated cells in regulation of fear behaviors

27. **Smith NJ, Trott JM, and Fanselow MS**, *(UCLA and Staglin Center for Brain & Behavioral Health, Department of Psychology, UCLA, Los Angeles, CA 90095)*. Fear, Avoidance and Punishment: Contribution of Pavlovian vs. Instrumental Processes

28. **Horenstein K, Chowdhury A, Lipatova O, Campolattaro MM**, *(Christopher Newport University)*. Transfer of Associative Responding Between Off and On Cues

29. **Kirry AJ, Twining RC, Gilmartin MR**, *(Marquette University, Milwaukee, WI)*. Prelimbic input to the basolateral amygdala is needed early in the acquisition of trace fear conditioning.

30. **Kwapis JL, Alagbhand Y, KramÃąr EA, LÃşpez AJ, Vogel Ciernia A, White AO, Shu G, Rhee D, Michael CM, Montellier E, Liu Y, Magnan CN, Sassone-Corsi P, Baldi P, Matheos DP, Wood MA**, *(University of California, Irvine)*. Epigenetic regulation of the circadian gene Per1 contributes to age-related impairments in long-term memory

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***The following posters will be presented at Saturday's Poster Session.***

1. **Chen S, Ebitz B, Jeong J, Bindas S, Chu M, Mahamed Z, Hayden B, Grissom N**, *(University of Minnesota)*. A visual bandit task in mice reveals a female-specific strategy associated with enhanced acquisition of the optimal choice

2. **Lafferty DS, Petrovich GD**, *(Psychology, Boston College)*. The effect of context familiarity on context-induced appetitive renewal in male and female rats

3. **Laughlin L[1,2], Sears R[1,2], Campese V[3], Cain C[1,2]**, *([1]NYU School of Medicine, Department of Child & Adolescent Psychiatry, New York, NY 10016 [2]Nathan Kline Institute for Psychiatric Research, Emotional Brain Institute, Orangeburg, NY, 10962 [3]University of Evansville, Departments of Psychology and Neuroscience, Evansville, IN, 47722)*. Role of dorsolateral striatum in habitual active avoidance responding

4. **Lebonville CL, Wangler LM, Jones ME, Paniccia JE, Parekh SV, Fuchs RA, Lysle DT**, *(Psychology and Neuroscience, UNC-Chapel Hill; Integrative Physiology and Neuroscience, Washington State University)*. Role of hippocampal outputs in context-heroin conditioned immune modulation

5. **Lensing A, Pajser A, Fisher H, Boerger R, Gilbert S, Lin H, Pickens C**, *(Kansas State University)*. The relationship of adolescent/early adult alcohol consumption and instrumental extinction learning

6. **Lingg RT, Johnson SB, Emmons EB, Anderson RM, Romig-Martin SA, Narayanan NS, LaLumiere RT, Radley JJ**, *(University of Iowa)*. Evidence for the involvement of the bed nucleus of the stria terminalis in memory consolidation

7. **Malvaez M, Shieh C, Murphy MD, Greenfield VY, Wassum KM**, *(Dept. of Psychology, UCLA, Los Angeles, CA 90095)*. Distinct cortical-amygdala projections drive reward value encoding and retrieval

8. **Manzano Nieves G, Johnsen A, Bravo M, Bath KG**, *(Brown University)*. Early life stress is associated with precocious amygdala development but delayed prefrontal development

9. **McReynolds JR, Schaps B, Wolf CP, Mathy JC, Hillard CJ, Mantsch JR**, *(Department of Biomedical Science, Marquette University, Milwaukee WI; Department of Pharmacology & Toxicology and Neuroscience Research Center, Medical College of Wisconsin, Milwaukee, WI)*. Role of mesolimbic endocannabinoid signaling in chronic electric footshock stress-induced escalation of cocaine intake in rats

10. **Meyer HC, Lee FS**, *(Weill Cornell Medicine)*. Developmental contributions of prefrontal and hippocampal circuitry to conditioned safety

11. **Mohammadmirzaei N, Della Valle R, Knox D**, *(University of Delaware )*. Effects of traumatic stress on fear and extinction memory in the conditioned suppression paradigm.

12. **Muller Ewald VA, LaLumiere RT**, *(Department of Psychological and Brain Sciences, Interdisciplinary Neuroscience Program, University of Iowa, Iowa City, IA)*. When to seek and when to stop: changes in rodent infralimbic cortical neuronal activity during extinction learning following cocaine self-administration

13. **Nett KE, Alizo V, LaLumiere RT**, *(Interdisciplinary Graduate Program in Neuroscience, Department of Psychological and Brain Sciences)*. Model of craving for high-fat/high-sugar food in rats

14. **Ng KH, Sangha S**, *(Purdue University , department of psychological sciences, Purdue Institute for Integrative Neuroscience)*. Changes in infralimbic cortical activity during conditioned inhibition of fear

15. **Orsi SA, Devulapalli RK, Surineni R, Jarome TJ**, *(Animal and Poultry Sciences and School of Neuroscience, Virginia Polytechnic Institute and State University)*. Distinct subcellular changes in proteasome activity and linkage-specific protein polyubiquitination in the amygdala during the consolidation and reconsolidation of a fear memory

16. **Pajser A, Foster C, Weston A, Pickens CL**, *(Kansas State University )*. Naltrexone administration during extended fear conditioning prevents low pre-incubated fear in the fear incubation model

17. **Plakke B, McKinnell Z, Barton P, Starr M**, *(Kansas State Univ. Dept of Psychological Sci)*. VPA (Valproic Acid) Model of Autism like behavior in Long-Evans Rats.

18. **Rankin, CH, Yu, AJ, Ardiel EL**, *(University of British Columbia)*. Parallel and Differential Neuropeptide Signalling Pathways Mediate Short-Term Sensitization in Caenorhabditis elegans

19. **Ray MH, Russ AN, Eghosa EK, Lee E, McDannald MA**, *(Boston College)*. Roles for the nucleus accumbens core, and its Gad1 subpopulation, in adaptive scaling of fear

20. **Santori A, Colucci P, Marinelli N, Morena M, Hill MN, Campolongo P**, *(Sapienza University of Rome; Hotchkiss Brain Institute, University of Calgary)*. Endocannabinoid modulation of circadian- and stress-dependent effects on rat short-term memory

21. **Shilyansky C, Young NP, Ramakrishnan C, Quirin S, Deisseroth K**, *(Stanford, PAVA MIRECC)*. Optical interrogation of memory related activity across the rodent default mode network

22. **Shipman ML, Bouton ME, Green JT**, *(University of Vermont)*. Chemogenetic inhibition of prelimbic cortex projections to dorsomedial striatum attenuates operant responding

23. **Stern SA, Azevedo EP, Doerig K, Pomeranz LE, Friedman JM**, *(The Rockefeller University)*. A molecularly defined insular→central amygdala circuit controls cue-mediated overconsumption

24. **Tavakkoli A, Bucci DJ, Todd TP**, *(Department of Psychological and Brain Sciences Dartmouth College, Hanover, NH)*. Pre-training lesions of dorsal hippocampus do not weaken ABC renewal of conditioned suppression

25. **Urien L, Cohen S, Jinich S, Nordlicht R, Bauer EP**, *(Barnard College)*. Contextual fear conditioning differentially activates extended amygdala circuits in male and female rats

26. **Vega Villar, M, Horvitz, JC, Nicola, SM**, *(The Graduate Center, CUNY, New York, NY; Dept. of Neuroscience, Albert Einstein College of Medicine, Bronx, NY.)*. Acquisition of a cued approach response requires NMDA receptor-dependent potentiation of cue-evoked excitations in the nucleus accumbens core.

27. **Wahlstrom KL, LaLumiere RT**, *(University of Iowa)*. Basolateral amygdala inputs to the medial entorhinal cortex in the consolidation of spatial and cued-response memory

28. **Yan A, Walsh E, Ghodsi S, Lederman JD, Chatterjee S, Abel T**, *(University of Iowa)*. Transgenic Mice Expressing a Dominant Negative Form of the NR4A Transcription Factor Exhibit Spatial Memory Deficits

29. **Zeid D, Kutlu MG, Gould TJ**, *(Penn State University, Department of Biobehavioral Health )*. Differential susceptibility to effects of acute versus chronic nicotine on fear extinction and spontaneous recovery in adolescent mice

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## Abstracts

*Listed in alphabetical order by first author's last name.*

**Abbott PW, Heskje J, Walsh K, Wu S, Hardie J, Freeman J, Bassuk AG, Parker KL**, University of Iowa. *Cerebellar abnormalities and changes in eyelid conditioned responses in the prickle2 mouse model of autism-like behavior*

Autism spectrum disorders (ASD) involve abnormalities across brain systems, resulting in a constellation of symptoms including behavioral inflexibility, cognitive dysfunction, learning impairment, altered social interactions, and perceptive time difficulties. Recently, it was discovered that a common gene variant involved in non-canonical Wnt signaling, prickle2, was present in a subset of individuals with ASD. Corroborated findings in prickle2 knock-out and heterozygous mice suggest patterns of behavior similar to individuals with ASD including altered social interaction on the three-chambered social task and behavioral inflexibility on the Barnes maze. Additionally, prickle2 disruption results in hippocampal neuronal abnormalities including reduced dendritic branching, synapse number, and post-synaptic density size. Prickle2 is strongly expressed in Purkinje cells. Our preliminary results indicate that there is a decrease in calbindin binding in cerebellar Purkinje cells. The canonical way to investigate cerebellar function in animals is using cerebellar dependent eyeblink conditioning. We hypothesize that if the cerebellum is abnormal in autism and in the Prickle2 animals, we will see impaired learning and/or expression of eyeblink conditioning. We examined eyeblink conditioning in prickle2-disrupted mice using a 275-millisecond light cue conditioned stimulus with a co-terminating 50 millisecond shock to the eyelid muscle as the unconditioned stimulus. Preliminary data suggest that prickle2-disrupted mice may have impaired acquisition of eyeblink conditioning while there are no significant impairments on a battery of motor tasks suggests. Additionally, we explored structural and physiological abnormalities in animals with prickle2 disruption using immunohistochemistry and whole Purkinje cell patch clamp recordings. These data will illuminate if Prickle2 animals have impairments in Purkinje cell structure and function and how these abnormalities may contribute to impairments in cerebellar dependent eyeblink conditioning.

**Abel T**, Iowa Neuroscience Institute. *Epigenetic Mechanisms of Long-Term Memory Storage*

Research in the Abel lab at the University of Iowa focuses on the molecular mechanisms underlying the persistence of memory. New experiences are initially encoded as labile short-term memories, which are converted into stable long-term memory by gene transcription-dependent processes during memory consolidation. In the hours after learning, the induction of gene expression follows a specific pattern that involves transient waves of transcriptional activity, which are needed for memory consolidation. This transcriptional regulation is meditated by epigenomic mechanisms such as histone acetylation and DNA methylation. These epigenetic modifications are critical for the long-lasting regulation of gene expression during development and may be a major mechanism of information storage in the brain. Changes in these epigenetic modifications may contribute to impairments in synaptic plasticity and cognitive function associated with many neurodevelopmental and neuropsychiatric disorders. Histone acetylation in an important epigenetic mark and our recent work has shown that the metabolic enzyme acetyl-CoA synthetase 2 (ACSS2) directly regulates histone acetylation important for long-term spatial memory. ACSS2 is present in the nucleus where it generated acetyl co-A 'on-site' at chromatin for histone acetylation and the transcription of key neuronal genes. Our work suggests that epigenetic modifications are a critical component of both synaptic plasticity and memory formation and storage, and we are working to identify the genes targeted by these epigenetic regulatory processes. We are examining the role of the NR4A orphan nuclear receptors, which are critical for long-term memory. Our understanding of the master transcriptional regulatory proteins involved in the consolidation and storage of long- term memory

may ultimately lead to the development of new treatments for the debilitating cognitive deficits associated with psychiatric disorders such as schizophrenia, bipolar disorder, post-traumatic stress disorder, autism and depression.

**Agee LA, Monfils MH**, UT Austin. *Effect of Demonstrator Reliability and Recency of Last Demonstration on Acquisition of a Socially Transmitted Food Preference*
In the social transmission of food preference paradigm, naÃŕve observer rats acquire safety information about novel food sources in the environment through social interaction with a demonstrator rat that has recently eaten said food. Research into the behavioural mechanisms governing this form of learning has found that observers show increased reliance on socially acquired information when the state of the environment makes personal examination of their surroundings risky. We aimed to (1) determine whether reliance on social information would decrease if previous reliance on social learning was unsuccessful and (2) whether reliance on the specific demonstrator that had transmitted poor information would similarly decrease. By inducing illness in observers following consumption of a socially demonstrated food, we created an environmental situation in which reliance on socially acquired information was maladaptive. We found that under these conditions, observers showed no change in their reliance on a specific demonstrator or socially learned information in general. Our experiment also unexpectedly produced results showing that demonstrators that had been more recently learned from were more influential in later transmissions that demonstrators that had been learned from less recently. Notably, this effect only emerged when the observer simultaneously interacted with both demonstrators, indicating that demonstrators must be in direct competition for this effect to manifest.

**Allen, MT, Myers, CE, & Servatius, RJ**, Univ. of Northern Colorado; Stress and Motivated Behavior Institute;Dept. of Veterans Affairs . *Schedules of partial reinforcement with us alone trials do not disrupt classical eyeblink conditioning: empirical and computational findings*
Schedules of partial reinforcement with CS-alone trials interleaved into CS-US paired training have typically disrupted acquisition of the tone-air puff association in eyeblink conditioning in humans. However, recent work has shown that CS-US learning is not slowed by interleaved US-alone trials. This discrepancy is surprising since both partial reinforcement protocols reduce the total number of paired CS-US trials. Previously, Kimble et al. (1955) reported that inserting a block of 20 US-alone trials during CS-US training did not disrupt eyeblink acquisition. Here, we sought to replicate and extend these findings by comparing interleaved vs. blocked US-alone trials during CS-US paired training in both humans and in a computational mode. Ninety-seven undergraduates volunteered for this experiment for research credit. Participants received 60 acquisition trials, consisting of either 100% CS tone-US air puff paired trials, 50% US-alone trials intermixed with CS-US paired trials, or a block of 20 US-alone trials inserted between blocks of 20 CS-US trials. We utilized a previously published computational model of hippocampal and cerebellar learning (Myers et al., 1998) which simulates many features of eyeblink conditioning to test the effects of these US-alone protocols. Both empirical and computational results supported the finding that US-alone trials, either intermixed or inserted as a block of 20 trials, do not disrupt acquisition of conditioned eyeblinks. Possible neural substrates of these US-alone effects involving the inferior olive circuit are discussed. - This work was supported by the Stress and Motivated Behavior Institute.

**Amy Yan, Emily Walsh, Saaman Ghodsi, Joseph D Lederman, Snehajyoti Chatterjee and Ted Abel**, University of Iowa. *Transgenic Mice Expressing a Dominant Negative Form of the NR4A Transcription Factor Exhibit Spatial Memory Deficits*
Memory consolidation requires waves of transcriptional events. Previous work in our lab found that all three members of the Nr4A subfamily of transcription factors (Nr4A1, Nr4A2, and Nr4A3) are upregulated following learning in the hippocampus. This project aimed to characterize the role of Nr4A transcription factors in hippocampus-dependent spatial memory. We utilized spatial object recognition (SOR) and Barnes maze tasks to assess cognitive performance, and rotarod to assess motor function, in a transgenic mouse model expressing a dominant negative form of Nr4A (Nr4ADN) in excitatory neurons. Nr4ADN forms dimers with Nr4A1 and Nr4A2 to block transcription of downstream genes. We found that Nr4ADN mice are impaired in long-term memory in SOR task. Nr4ADN mice showed normal learning in Barnes maze, but showed deficits to reach the target hole during probe test. Our rotarod task showed no significant differences between Nr4ADN and controls, suggesting normal motor coordination. These results demonstrate the importance of the Nr4A family of transcription factors in hippocampus-dependent long-term spatial memory. - Funding provided by NIH R01 MH087463 to Ted Abel and Nellie Ball Trust to Snehajyoti Chatterjee âĂć Acknowledgements to the Neural circuit and behavior core (University of Iowa).

**Bral SR, Farley SJ, Freeman JH**, The University of Iowa. *Amygdala central nucleus inactivation impairs acquisition and retention of delay eyeblink conditioning in female rats*
Amygdala central nucleus (CeA) pharmacological or optogenetic inactivation impairs cerebellar-dependent eyeblink conditioning (EBC) in male rats (Farley 2016, 2017, 2018). While previous studies suggest sex differences during EBC in a context implicating amygdala involvement (Shors 1998), it is currently unknown if bilateral CeA inactivation in female rats cause similar cerebellar learning impairments as in male rats. In this study, adult female rats underwent delay EBC (tone, conditioned stimulus; periorbital shock, unconditioned stimulus) with either muscimol (GABA-A agonist) or saline infusions for the first five training sessions. Non-infusion sessions commenced from session 6 until animals reached an 80% CR criterion. All rats were then subject to a counterbalanced order of saline and muscimol retention sessions. Bilateral CeA inactivation significantly impaired acquisition and retention of EBC. CR percentage in session 6 for the muscimol group was not different than in session 1 for the saline group, i.e. no savings. Both groups reached an equal level of conditioned responses before retention tests. Additionally, both groups were equally impaired during muscimol retention. Saline retention revealed the same level of conditioned responses as the criterion session for both groups. These results closely mirror our previous results in adult male rats. Overall, it suggests that the amygdala's modulatory role in cerebel-

lar dependent learning is similar for male and females. - National Institute of Neurological Disorders and Stroke grant NS088567

**Broschard MB, Kim J, Love BC, Wasserman EA, Freeman JH**, Dept of Psychological Brain Sciences, UIowa. *Rule-Based and Information Integration Category Learning in Rats*
The COVIS (Competition between Verbal and Implicit Systems) model postulates two systems in humans that learn new categories: a declarative system that mediates rule-based (RB) tasks and a non-declarative system that mediates information integration (II) tasks. Humans and monkeys, but not pigeons, learn RB tasks faster than II tasks; however, it is unknown whether this advantage is unique to primates. Therefore, we trained rats on RB and II tasks using circular stimuli with black and white gratings that differed in spatial frequency and orientation. For the RB groups, category distributions were calculated according to the relevant dimension (either spatial frequency or orientation). These distributions were rotated 45 degrees to create the II tasks. Similar to pigeons, no difference in learning rate was observed between RB and II groups. Testing sessions used broader distributions to assess category generalization, and no difference in category generalization were observed between RB and II groups. These findings, together with decision boundary analysis using General Recognition Theory (GRT), highlight the limitations of executive function in rats. However, fitting the generalization data to the Generalized Context Model (GCM) revealed a dissociation in attention allocation between groups. Specifically, rats used selective attention to learn RB tasks and equal attention to both dimensions to learn the II tasks. Together, we propose that rats can use selective attention in category learning, but do not use rules as primates do.

**Burwell, Rebecca D.**, Brown University. *The neural circuitry of spatial context: Beyond the hippocampus*
Representations of context are important for perception, memory, decision-making, and other cognitive processes. There is considerable evidence that the use of contextual representations is disrupted in a number of neuropsychiatric and neurological disorders. Yet, there is disagreement about how and where context is represented in the brain. A prominent theory of the medial temporal lobe memory system posits that object information reaches the hippocampus via the perirhinal cortex, spatial and contextual information arrive via the postrhinal cortex, and the hippocampus binds object and spatial information into memories. By one view, the spatial pathway conveys both spatial and contextual information. By another view, representations of context are configured in the hippocampus, itself. I will present evidence that that spatial context is represented upstream of the hippocampus in the postrhinal cortex and that these representations rely on direct input from the perirhinal cortex. - NIMH R01MH108729 and NSF IOS-1656488

**Castro, L, Wasserman EA**, The University of Iowa. *Memory demands and cognitive flexibility in pigeons*
Pigeons can show remarkable cognitive flexibility, evidenced by their rapid, on-demand switching between different categorization tasks, using the same set of stimuli, within the same training session (Castro & Wasserman, 2016). But cognitive flexibility in pigeons can also be challenged, as we recently showed by using a proactive-retroactive interference experimental design (Darby, Castro, Wasserman, & Sloutsky, 2018); rather than rapidly adjusting their behavior to changing stimulus-response contingencies, pigeons tended to perseverate when presented with shifts across phases. It seems that concurrent training on different contingencies allows the creation of strong long-term memory representations that help rapid and flexible behavior (Castro & Wasserman, 2016). However, successive training on different contingencies results in competition between the old contingencies represented in long-term memory and the new contingencies that need to be maintained in working memory (Darby et al., 2018); failure to inhibit the old contingencies and maintain the new contingencies in memory leads to perseveration and diminished cognitive flexibility.

**Chaudhri N, Valyear M, Sciascia J, Khoo S.**, Concordia University. *Context as a critical cue for alcohol: striatal and amygdala mechanisms*
The recreational use of alcohol can escalate into problematic drinking and alcohol use disorders. Alcohol-seeking and drinking are profoundly influenced by environmental cues that predict alcohol. I will describe a preclinical model that my laboratory developed to study the psychological and neural processes that regulate cue- and context-triggered alcohol-seeking. We report that contexts associated with alcohol have a robust and enduring impact on alcohol-seeking and relapse. Using a pathway-specific, chemogenetic approach in transgenic rats, we show that dopamine is a critical substrate for cue-triggered alcohol-seeking, and that there is a dissociation at the level of the nucleus accumbens in the role that dopamine plays in responding to different types of alcohol cues. The nucleus accumbens receives input from the basolateral amygdala, a brain region that is critically implicated in cue-reward learning. I will present data on the involvement of glutamatergic transmission in the basolateral amygdala in cue-triggered alcohol-seeking. By defining the psychological and neural mechanisms that mediate cue-triggered alcohol-seeking we seek to advance our fundamental knowledge of these processes and propel new treatments for alcohol use disorders. - CIHR, FRQS, Concordia University

**Chen S, Ebitz B, Jeong J, Bindas S, Chu M, Mahamed Z, Hayden B, Grissom N**, University of Minnesota. *A visual bandit task in mice reveals a female-specific strategy associated with enhanced acquisition of the optimal choice*
Neurodevelopmental disorders, such as autism spectrum disorders (ASD), have a strong male bias in diagnosis, and are associated with challenges in learning to predict positive outcomes of behavior. Do sex-specific mechanisms of goal-directed learning contribute to the male-specific vulnerability to ASD? One commonly used task, the multi-armed bandit, examines the dynamics of reinforcement learning and decision making, requiring a person or animal to choose each trial between exploitation of a previously experienced option, versus exploration of other options with unknown, but potentially more rewarding, outcomes. Visually cued bandit tasks have been widely employed in humans and nonhuman primates, but are largely unused in rodents. This has limited the ability to understand the neural mechanisms of complex reward environments in rodent models. We used a two-arm bandit task in

thirty-two 129/B6 F1 mice (16 male and 16 female) to examine whether there are baseline sex differences in the ability to learning the reward probabilities associated with two visual cues presented on a touchscreen (80% chance of payoff versus 20%). Female mice learned to choose the cue associated with the higher probability of reward faster. A multiple linear regression analysis revealed that female mice relied more on spatial repetition in decision making at the early stage of learning, but switched from this strategy to using information of reward outcome of cues more rapidly than did male mice. We wished to examine neural mechanisms that might support these sex differences in strategy selection. Animals were sacrificed immediately following behavior on their final test day, and c-fos gene expression was used as a proxy for neural activity. In the nucleus accumbens, fos expression was more lateralized in females, while in males expression was equal between left and right accumbens. This suggests that more lateralized activation of the brain in females may drive female-specific decision making strategies that result in faster learning, and may shed light on sex-specific mechanisms in neurodevelopmental disorders.

**Crystal JD**, Indiana University. *Animal models of episodic memory*

People retrieve episodic memories about specific earlier events that happened to them. Accordingly, researchers have sought to evaluate the hypothesis that nonhumans retrieve episodic memories. The central hypothesis of 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. We tested this hypothesis by ruling out non-episodic memory hypotheses. We developed a range of approaches, so that we have working models to evaluate elements of episodic memory in animals. These 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); multiple item-in-context memories (Panoz-Brown et al., 2016, Current Biology); replay of episodic memories (Panoz-Brown et al., 2018, Current Biology); and answering unexpected questions after incidental encoding (Zhou, Hohmann, & Crystal 2012, Current Biology). In each approach, evidence for episodic memory comes from studies in which judgments of familiarity cannot produce accurate choices in memory assessments. These approaches may be used to explore the evolution of memory. - AG053524 and AG051753

**De Corte BJ & Matell MS**, University of Iowa, Iowa Neuroscience Institute; Villanova University, Department of Psychology. *The times they are a changin': Temporal covariance and the common cause hypothesis*

Individuals must predict future events to proactively guide their behavior. Predicting when events will occur is a critical component of these expectations. Temporal expectations are typically generated based on individual cue-duration relationships. However, in the environment, the durations associated with different cues often co-vary due to a common causal factor. We asked whether observers calibrate their temporal expectations based on this expected covariance, which we refer to as the 'common cause hypothesis'. To assess this, we trained rats on the peak-interval procedure, in which distinct cues predicted reward availability for making an operant response after different durations elapsed (e.g., Cue 1: 8s / Cue 2: 16s). We then changed the reinforcement-duration for one of the cues and tested how this would impact responding for the other (unchanged) cue. Experiments 1 and 2 confirmed that, when the duration associated with one temporal cue changes, timed-responding to the unchanged cue shifts in the same direction, as if rats anticipated that the durations associated with the two cues would covary. Experiment 3 showed that this transfer effect is blocked when subjects are trained that expecting covariance among different temporal cues is not appropriate in a given situation. In Experiment 4, we confirmed that the transfer depends on the environmental context in which a duration-change occurs. Finally, Experiments 5 and 6 were controls showing (respectively) that duration-changes are necessary to produce the transfer and that introducing novel cues associated with previously un-experienced durations does not account for the effect. These results reveal a novel principle for generating temporal expectations and pose a challenge to existing timing models.

**de Solis CA, Gonzalez Cuauhtémoc U, Galdamez MA, Samuel W. Woodard SW, Carlos E. Salinas CE, Joel N. Miller JN, Hajira Elahl H, Pineda OH, Perish JM, Oad S, Gatica de las Fuentes S, Owen MS, Sandoval Jr. A, Holehonnur R, Ploski JE**, The University of Texas at Dallas, Columbia University . *Overexpression of GluN2B(E1479Q) Within The Basal and Lateral Amygdala Enables The Modification of Strong Reconsolidation Resistant Fear Memories*

Memory retrieval does not initiate the reconsolidation process for some memories rendering pharmacotherapies designed to disrupt reconsolidation ineffective (Wang et al., 2009; Winters et al., 2009). Disruption of strong memories have been shown to be problematic using reconsolidation blockade, and this is likely due to the inability of these memories to destabilize upon retrieval. In an effort to understand the molecular basis for why weak and strong fear memories differ in their requirements to initiate reconsolidation, we recently determined that training-dependent changes in the N-methyl D-aspartate receptor (NMDAR) subunit composition occur at basal and lateral amygdala (BLA) synapses that correlate with a strong memory's inability to be modified upon retrieval. We then demonstrated that genetically increasing the NMDAR GluN2A/GluN2B ratio is sufficient to block retrieval-induced memory destabilization and this prevents an existing memory trace from being modified via reconsolidation updating. Here we demonstrate that increasing synaptic GluN2B levels within BLA excitatory neurons enables strong memories to be modified via reconsolidation. To accomplish this, we generated lentiviruses designed to express GluN2B or GluN2B(E1479Q) from a TRE3G promoter. Injecting these viruses into the BLA of Îś-CaMKII-tTA mice allows us to restrict expression of the GluN2B transgenes to excitatory neurons and also enables expression of the transgene to be selectively expressed before or after fear conditioning training using doxycycline (Dox) (Holehonnur et al., 2016). GluN2B(E1479Q) contains a point mutation in the PDZ domain of GluN2B which leads to higher surface levels. To create a strong fear memory, we trained animals on Pavlovian auditory fear conditioning using ten tone-shock pairings (10TSP; Shock- 2 sec, 0.75mA; Tone- 30 sec, 75 dB, 5khz). Increasing GluN2B at the time of memory retrieval with GluN2B(E1479Q), but not GluN2B(WT), allowed for pharmacologically induced am-

nesia of a strong fear memory. This occurrence of retrograde amnesia was found to be dependent on retrieval and resistant to spontaneous recovery when examined seven days following PR-LTM. Overexpression of GluN2B(E1479Q) at the time of memory retrieval had no effects on reconsolidation of weak fear memories. In addition, we determined that neither overexpression of GluN2B(WT) or GluN2B(E1479Q) influences fear memory extinction or maintenance of the memory. Fear memory consolidation, however, is enhanced if GluN2B(E1479Q) was overexpressed in the BLA at the time of training.

**Dulka BN, Bagetalas ED, Bress, KS, Cooper, MA**, University of Tennessee. *Chemogenetic Activation of an Infralimbic Cortex to Basolateral Amygdala Neural Projection is Sufficient for Resistance to Conditioned Defeat*

Stress is a contributing factor in the development of several mood and anxiety disorders, although there are significant individual differences in vulnerability. Animal models of social defeat are used to investigate the biological basis of stress susceptibility and resilience. Male Syrian hamsters are highly aggressive and territorial, but after social defeat they exhibit a conditioned defeat (CD) response which is characterized by increased submissive behavior and a failure to defend their home territory in a social interaction test with a smaller, non-aggressive intruder. Hamsters that achieve social dominance show resistance to CD as well as increased defeat-induced neural activity in infralimbic (IL) neurons that send efferent projections to the basolateral amygdala (BLA) compared to subordinates and controls. In the current study, we aimed to determine if selective activation of IL-to-BLA projections using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) is sufficient to produce CD resistance in subordinate hamsters. To answer this question, we used a dual-virus approach and injected a Cre-dependent Gq DREADD virus into the IL and a retrograde Cre virus into the BLA. First, we verified that clozapine-N-oxide (CNO), the drug that activates the Gq receptor, itself has no effect on CD behavior. Next, the dual-virus approach was validated by showing that CNO treatment increased c-Fos immunoreactivity in the IL. Finally, we tested whether CNO-treated subordinate hamsters would show a reduced CD response compared to vehicle-treated subordinates. We indeed found that CNO treatment reduces the CD response in both subordinate and control hamsters. This project extends our understanding of the neural circuits underlying resistance to social stress, which is an important step towards delineating a circuit-based approach for the prevention and treatment of stress-related psychopathology. - NIH R15 MH107007

**Escobedo A, Sowinski EM, Herakovich R, Sangha S**, Purdue University - Department of Psychological Sciences, Purdue Institute for Integrative Neuroscience. *The effect of the partial NMDAR agonist D-Cycloserine on conditioned inhibition of fear*

Learning to inhibit fear and maintain reduced fear levels to non-threatening environmental cues is a constant challenge for individuals suffering from posttraumatic stress disorder (PTSD). PTSD individuals have difficulty maintaining reduced fear levels after extinction-based therapies, and are also impaired in learning to inhibit fear to explicit safety cues trained under conditioned inhibition paradigms. Prior research has shown the beneficial effects of exposure therapy in reducing fear can be facilitated by the partial NMDA receptor agonist, D-Cycloserine (DCS). However, it is unclear if DCS is facilitating fear versus safety discrimination or if it is promoting non-specific fear reduction. Thus, the present study examined the effects of DCS in adult male Long Evans rats during a fear, safety, and reward cue discrimination conditioning task (DC) that is well-established in our laboratory. In this DC task, rats are exposed to pairings of a) a fear cue with shock, b) a safety cue with no shock, c) a reward cue with sucrose, and most importantly, d) a compound fear+safety cue with no shock. Adult male rats typically show significant inhibition of freezing to the compound fear+safety cue compared to the fear cue during the 3rd discrimination session. In this study, we hypothesized that DCS would facilitate discrimination learning between the fear cue and the fear+safety cue during earlier discrimination sessions, and that this improved discrimination may facilitate subsequent fear extinction under drug-free conditions. DCS (30.0 mg/kg i.p) was administered during the first three of four DC sessions. Saline was administered during the last DC session, to assess behavior under drug-free conditions, and subsequent extinction. As is typical, the saline group showed significant inhibition of fear during DC3, but preliminary data suggests the level of inhibition to the fear+safety cue versus the fear cue may be greater in DCS group. Based on our preliminary data it does not appear this improved fear versus fear+safety cue discrimination has any beneficial effects on subsequent fear extinction, as both saline and DCS groups showed similar fear extinction curves. This may suggest extinction and conditioned inhibition are mediated by different mechanisms. - This work was supported by the National Institute of Mental Health under award number R01MH110425

**Farley SJ, Freeman JH**, The University of Iowa. *Amygdala central nucleus inactivation impairs learning-related spike activity and local field potentials in the basilar pontine nucleus*

Accumulating evidence shows that amygdala central nucleus (CeA) output to the basilar pontine nucleus (BPN) may function as a modulator of sensory information to the cerebellum (Farley 2016, 2018; Pochiro 2015; Siegel 2015; Taub 2010). Additionally, pharmacological inactivation of the CeA during eyeblink conditioning reveals that conditioned responses (CRs) are strongly attenuated and only modest levels of acquisition occur without CeA input (Farley 2018). In this study, we recorded single unit and local field potential (LFP) activity in the BPN of adult rats as they were trained in the cerebellum-dependent task, delay eyeblink conditioning. In this task, a neutral conditioned stimulus (CS; 2 kHz tone, 400ms duration) is paired with an unconditioned stimulus (US; 2.5 mA periorbital stimulus). We first analyzed pontine baseline LFP activity with and without bilateral CeA inactivation using the GABAA agonist, muscimol (2mM). A stable recording was acquired, muscimol infused, and then recording continued following a brief diffusion period. After 48 hours, rats were subsequently exposed to a counter-balanced order of saline or muscimol CS-alone sessions (50-trials) while recording BPN spike and LPF activity. Following CS alone sessions, rats were then randomly divided into muscimol or saline groups for training in delay eyeblink conditioning. Bilateral infusions to the CeA occurred before each of the first 5 eyeblink sessions (100-trials/session). Training continued without infusions from session 6 until reaching an 80% CR criterion. After criterion, rats completed counter-balanced muscimol or saline retention

sessions. CeA inactivation modulated behavioral CRs and neural activity in the BPN. Accompanying the impairment in CRs, BPN spike activity, which was CS-responsive under the vehicle control sessions, was significantly decreased when CeA was inactivated by muscimol. BPN LFP signals also showed the notable modulation by CeA activation/inactivation. Specifically, CeA inactivation resulted in the most significant decreases in the alpha (12 – 18 Hz) and beta (20 – 30 Hz) bands. To a lesser extent, LFP power also decreased in the theta (4-8 Hz) band. The results suggest that the CeA modulation of learning and neural activity in BPN might occur via higher frequency bands. - National Institute of Neurological Disorders and Stroke grant NS088567

**Ferrara NC, Trask S, Cullen PK, Pullins, SE, & Helmstetter FJ**, Department of Psychology, University of Wisconsin-Milwaukee. *Inhibition of thalamic terminals in the amygdala may facilitate extinction learning*

Fear memory formation is characterized by increased excitatory synaptic strength between primary auditory areas (i.e., the auditory thalamus (MgN) and auditory cortex) and the amygdala. The strength of these connections is increased as a result of learning, and the retention of auditory fear is dependent on the maintenance of potentiated cortico- and thalamo-amygdala synapses. Extinction has been viewed as an inhibitory learning process that results in a context-specific decrease in fear responding due to increased inhibition in the amygdala. Input from the medial prefrontal cortex is thought to be a primary factor driving elevated inhibition through strengthened connections with local interneurons. This increased inhibition is associated with several plasticity related events in the amygdala, such as maintained potentiation of cortico- and thalamo-amygdala connections and decreased phosphorylation of cAMP response element-binding protein (CREB), that may provide molecular correlates for extinction. Here we study the role of the thalamo-amygdala pathway during fear recall. We silenced input from the MgN to the amygdala using the light driven proton pump, ArchT (AAV9-CAG-ArchT-GFP). We found that MgN driven activity in the amygdala is critical during auditory fear retrieval and when silenced during retrieval, impairs fear assessed during a long-term test. This suggests activity in the thalamo-amygdala pathway is necessary to maintain fear responding at remote time points. Additionally, fear renewed in the training context, demonstrating a context-specific reduction in fear independent of thalamo-amygdala silencing. Groups that did not receive contiguous CS presentations with optogenetic inhibition during retrieval did not show reductions in fear during retrieval or test, suggesting inhibition of MgN-amygdala terminals is specifically required during memory reactivation. Phosphorylation of CREB was measured and quantified following initial retrieval, LTM test, and renewal. Groups that received MgN-LA terminal silencing during retrieval showed reduced phosphorylated CREB after retrieval and test, but not following renewal. We next measured the synaptic expression of AMPA receptors in the amygdala after MgN-amygdala inhibition and did not find differences in the expression of GluR1 or GluR2 subunits, suggesting the decrease in fear responding was not due to a loss of potentiated amygdala synapses. Together, these results suggest inhibition of MgN activity in the amygdala during recall can facilitate extinction learning. - NIMH R01 MH069558

**Ferri SL, Lee JY, Dow H, Brodkin ES, Abel T** , University of Iowa, University of Pennsylvania. *Fear conditioning deficits in the Pcdh10 mouse model relevant to autism*

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects nearly five times as many males as females. The protocadherin 10 gene (PCDH10) has been associated with ASD and is highly expressed in the amygdala and striatum. It encodes for an activity-dependent cell adhesion molecule involved in dendritic spine development. We previously reported that juvenile male mice (28-32 d) heterozygous for a deletion of Pcdh10 (Pcdh10+/-) exhibit deficits in a social approach task. Recently, we found that these deficits are ameliorated in adults (60-90 d), a phenomenon of social improvement also observed in individuals with autism. However, the cognitive deficits we have recently observed, in both contextual and cued fear conditioning, are present before and after puberty. These behavioral impairments, as well as amygdalar abnormalities we previously reported, including decreased expression of NMDAR and increased spine density, are observed in males only. Future studies will address the mechanisms involved in the age- and sex-specificity of the social and cognitive deficits. - Carver Trust

**Fisher H, Pajser A, Fox S, Long C, Gilbert S, Pickens CL**, Kansas State University . *Inactivation of the basolateral amygdala or mediodorsal thalamus but not orbitofrontal cortex during training impairs performance on a multiple-response/multiple-reinforcer operant devaluation task in rats.*

Devaluation is a task often used to model flexible goal-directed behavior, the ability to adaptively modify behavior when the value of a reinforcer changes. In rodents, there are many simplified versions of the devaluation task and the brain regions involved can differ depending on the task demands. We chose to use a multiple-response/multiple-reinforcer devaluation task that should require the basolateral amygdala (BLA), orbitofrontal cortex (OFC), and mediodorsal thalamus (MD). In order to determine the role of these brain areas in the learning the necessary associations, we inactivated each of these three brain regions during operant training and then tested the rats on devaluation without the brain areas inactivated. We implanted bilateral cannula into the BLA, OFC, or MD of male and female Long Evans rats. The rats then were trained on a multiple-response/multiple-reinforcer operant devaluation task. Five minutes prior to beginning each cued-trial training session, the rats were infused with either muscimol/baclofen (n= minimum of 6/group) or PBS (n=minimum of 8/group). We gave cued-trial operant training with lever-light compounds available during 40-sec trials. Two lever-light compounds were each associated with a different food pellet (earned for lever-pressing on an intermittent reinforcement schedule). Only one lever-light-food pellet combination was available during each training session. After the rats received four days of cued operant training, two days for each lever, each of the two reinforcers was devalued through selective satiety in two separate tests (one pellet sated in each test) and devaluation was assessed through choice tests in extinction. The control (PBS) and OFC inactivation groups showed a devaluation effect but the BLA or MD inactivation groups did not. These results show that the BLA and MD regions are involved in our devaluation task but the OFC is not. Future studies will determine whether intact devaluation in the OFC group reflects a different behavioral strategy than PBS rats, and whether prelimbic cortex inactivation would

impair devaluation in our task. - This work was supported by the National Institutes of Health [grant number P20 GM113109-01A1]

**Ghobbeh A, Taugher RJ, Alam S, Fan R, Lalumiere RT, Wemmie J**, University of Iowa, Department of Psychiatry. *A novel role for acid-sensing ion channel (ASIC1A) in Pavlovian reward conditioning*

Pavlovian fear conditioning has been shown to depend on ASIC1A, however it is unknown whether conditioning to rewarding stimuli also depends on ASIC1A. Here we tested the hypothesis that ASIC1A contributes to Pavlovian conditioning to a non-drug reward. We found effects of ASIC1A disruption depended on the relationship between the conditional stimulus (CS) and the unconditional stimulus (US), which was varied between five experiments. In experiment 1, when the CS preceded the US signaling an upcoming reward, $Asic1a^{-/-}$ mice exhibited a deficit in conditioning compared to $Asic1a^{+/+}$ mice. Alternatively, in experiment 2, when the CS co-initiated with the US and signaled immediate reward availability, the $Asic1a^{-/-}$ mice exhibited an increase in conditioned responses compared to $Asic1a^{+/+}$ mice, which contrasted with the deficits in the first experiment. Furthermore, in experiments 3 and 4, when the CS partially overlapped in time with the US, or the CS was shortened and co-initiated with the US, the $Asic1a^{-/-}$ mice did not differ from control mice. The contrasting outcomes were likely due to differences in conditioning because in experiment 5 neither the $Asic1a^{-/-}$ nor $Asic1a^{+/+}$ mice acquired conditioned responses when the CS and US were explicitly unpaired. Taken together, these results suggest that the effects of ASIC1A disruption on reward conditioning depend on the temporal relationship between the CS and US. Furthermore, these results suggest that ASIC1A plays a critical, yet nuanced role in Pavlovian conditioning. More research will be needed to deconstruct the roles of ASIC1A in these fundamental forms of learning and memory.

**Gironda SC, De Corte BJ, Matell MS**, Villanova University. *Relational encoding of time across modalities in the peak-interval procedure*

Previous work from our lab (De Corte et al., submitted) showed that rats recalibrate their temporal expectations of one cue-signaled duration, after being re-trained with a different cue-signaled duration. Specifically, subjects were trained on a peak-interval procedure that cue 1 (e.g., tone) signified an 8s fixed-interval, while cue 2 (e.g., light) indicated a 16s fixed-interval. In a subsequent re-training phase, cue 2's fixed interval was extended to 32s, and exposure to cue 1 was halted. After temporal control to cue 2 was established at the new peak time, testing of cue 1 revealed that subjects shifted their expectation for that cue in the same direction (i.e., a 59% rightward shift). To assess how this effect would generalize to other duration ratios, in experiment 1,âĂŕwe used a 4s interval for cue 1 and a 16sâĂŕintervalâĂŕfor cue 2. Following re-training of cue 2âĂŕto 32s, testing of cue 1 demonstrated no significant shift (%+/-). In Experiment 2, we trained separate groups rats on different interval ratios with cue 1 (tone) at 8 s, 12 s, or 24 s and cue 2 (light) at 16 s. Following re-training of cue 2 to 32s, we found that cue 1's rightward shift (as a percentage of initial peak time) grew in direct proportion to the initial temporal ratio between the two cues (r= .98, p<0.001). However, cue 1 shifts were significantly smaller than the 100% increase in cue 2 (p<??), suggesting that subjects tempered their recalibrated expectation by the initial, absolute, duration of cue 1.âĂŕ This evidence suggests that rats encode both the absolute and relative relationship between temporal cues from different modalities.

**Griffin A**, University of Delaware. *Hippocampal-thalamic-prefrontal circuit contributions to spatial working memory*

The hippocampus is thought to organize memories based on their spatial and temporal context, whereas the medial prefrontal cortex is known to support context-dependent memory retrieval. Thus, these structures must interact during spatial working memory, a process that requires the encoding of trial-unique information, organization of that information within a spatial-temporal context, and appropriate action selection. Based on anatomical work, we know that one major conduit by which HPC and mPFC are anatomically linked is through the ventral midline thalamic nuclei – reuniens (Re) and the adjacent rhomboid nucleus. Our lab has shown that both SWM and mPFC-HPC oscillatory synchrony depend on the functional integrity of the Re/Rh. Our lab has recently implemented optogenetic silencing techniques to identify which components of the mPFC-Re-HPC circuit are critical for encoding, maintenance, and retrieval of spatial information using a delayed-non-match-to-position task. We have found that silencing of Re and of dorsal HPC (dHPC) inputs to Re disrupts encoding. The mPFC-Re pathway is selectively involved in both encoding and retrieval. Consistent with the optogenetic results, multisite recordings of dHPC, Re, and mPFC during the DNMP task show that theta synchrony within the HPC-Re-mPFC circuit differs between encoding and retrieval. Moreover, dHPC leads Re selectively during encoding (vs. retrieval) and good (vs. poor) performance. Together, these results support the notion that Re is a critical component of the mPFC-HPC network and plays a significant role in functional interactions within this circuit. - NIMH, R01MH102394

**Grissom NM**, University of Minnesota. *Maximally divergent sex-specific strategies in decision making lead to more optimal performance in females*

Neurodevelopmental disorders, such as autism spectrum disorders (ASD), have a strong male bias in diagnosis, and are associated with challenges in learning to predict positive outcomes of behavior. Do sex- specific mechanisms of goal-directed learning contribute to the male-specific vulnerability to ASD? One commonly used task, the multi-armed bandit, examines the dynamics of reinforcement learning and decision making, requiring a person or animal to choose each trial between exploitation of a previously experienced option, versus exploration of other options with unknown, but potentially more rewarding, outcomes. Visually cued bandit tasks have been widely employed in humans and nonhuman primates, but are largely unused in rodents. This has limited the ability to understand the neural mechanisms of complex reward environments in rodent models. We used a touchscreen visual two-arm bandit task to examine whether there are baseline sex differences in the ability to learning the reward probabilities associated with two cues, testing each mouse over multiple cue pairs. Female mice learned to choose the cue associated with the higher probability of reward faster. A

multiple linear regression analysis revealed that female mice relied more on spatial repetition in decision making at the early stage of learning. This approach reduced the dimensions over which choices were made and thus permitted females to learn about the values of the cues more rapidly than male mice. In contrast, males appear to use a strategy that involves uniform or "random" choice selection and suggests the male brain weights novel information gathering more highly than consistency of choice or reinforcement. This suggests that increased response consistency may drive female-specific decision-making strategies that result in faster learning, and shed light on sex-specific mechanisms in neurodevelopmental disorders.

**Grissom, N.M, McKee, S.E., Schoch, H., Walsh, L. Nickl-Jockschat, T., Reyes, T.M., Abel, T.**, University of Iowa. *Deficits in learning are common across multiple mouse models of autism*
Autism Spectrum Disorders (ASDs) are a set of neurodevelopmental disorders that cover a wide range of symptoms. The overall prevalence of ASDs continues to increase and is 4 times more common in males than females. Given the role of striatal and cortical deficits in ASDs and the large discrepancy in prevalence rates, the current experiments will assess different genetic mouse models in distinct learning and memory paradigms. The mouse models may include 16p11.2 microdeletion animals, which is the most common genetic link with ASD, CNTNAP2 knockout animals, and Shank3b knockout animals. All models will be trained in several distinct behavioral paradigms including operant conditioning, fear conditioning, social activity, and novel object recognition. Preliminary data suggests deficits in mutant mice in reward learning procedures and potentially reduced motivation as measured by a progressive ratio task. Overall, these preliminary findings suggest impaired goal-directed learning in males of 3 different ASD-linked genotype mouse models. Continuing work will demonstrate the depth and breadth of the deficits seen in mutants across behavioral procedures and tasks. 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. - SIMONS Foundation

**Halverson HE, Mauk MD**, Center for Learning and Memory and Department of Neuroscience, University of Texas, Austin, Texas 78712. *Extinction and reacquisition of conditioned eyelid responses are controlled by eyelid Purkinje cells*
Acquisition and extinction of conditioned eyelid responses at the behavioral level appear to be opponent processes, extinction reverses acquisition. Extinction clearly does not erase the memory established during acquisition. For example, the rate of reacquisition after extinction is much faster than during initial learning. Learning dependent changes in eyelid Purkinje cells located at the base of the primary fissure control the trial-to-trial kinematics of conditioned eyelid responses. Eyelid Purkinje cells show complex spikes in response to the unconditioned stimulus (US) used during conditioning while all non-eyelid Purkinje cells show spontaneous complex spikes only. The current experiment used tetrode recordings of eyelid Purkinje cells to investigate if opponent processes in the cerebellum mediate extinction and reacquisition of conditioned eyelid responses within the same session. Rabbits were initially trained with delay conditioning (tone CS; eyelid stimulation US) with either a 500, 700 or 1000 ms inter-stimulus interval (ISI) while recording from at least one eyelid Purkinje cell. After robust conditioning was established at one of the three ISIs an extinction/reacquisition/extinction session was then given to investigate the relationship between eyelid responses and changes in Purkinje cell activity. These sessions consisted of 4 blocks (36 trials) of tone alone trials (extinction), followed by 2 blocks (18 trials) of tone and eyelid stimulation paired training (reacquisition) and finally 6 blocks (54 trials) of tone alone (extinction). At the beginning of the session conditioned eyelid responses and learning-dependent decreases in eyelid Purkinje cell activity extinguished at the same rate within the first 2 blocks for all three ISIs tested. Eyelid responses and decreases in Purkinje cell activity returned within a few trials during reacquisition and rapidly extinguished again in the last half of the session. The rate of extinction was the same with both tone and mossy fiber stimulation as the CS, indicating the cerebellum is likely mediating extinction in both cases. These results provide strong evidence indicating expression/extinction of conditioned eyelid responses are controlled by rapid opponent processes in a subset of Purkinje cells. - Grants MH46904, MH74006

**Hartley, Catherine A.** , New York University. *Control and the Calibration of Motivated Behavior*
The controllability of positive or negative environmental events has long been recognized as a critical factor determining their impact on an individual's motivated behavior. An extensive body of work in animal models suggests that controllable and uncontrollable reinforcement yield divergent effects on subsequent behavior. In this talk, I'll present studies demonstrating that the controllability of motivationally significant outcomes similarly modulates subsequent behavior in humans, and examine the neural mechanisms underlying these effects. I'll argue that estimates of agency, derived from one's experience of control, may be used to calibrate the nature of one's motivated behavior along a continuum ranging from proactive ('What can I do in this environment?') to reactive ('What will this environment do to me?'). - NARSAD, Klingenstein-Simons Fellowship, Jacobs Foundation

**Heiney SA[1], Medina JF[2]**, [1]University of Iowa, [2]Baylor College of Medicine. *Predictive control of a motor synergy by the cerebellum*
Some parts of the motor system are thought to be organized around ethologically-relevant synergistic movements of multiple body segments—so called "action maps". Action maps have been demonstrated for reactive motor control involving reflexive movements but they have not been demonstrated in the context of predictive motor control. Using a classic model of ethologically-relevant predictive motor learning, eyeblink conditioning, we demonstrate an action map for predictive motor control within the cerebellum. As mice learned this task, a wide network of muscles spanning multiple body segments were recruited in a complex and coordinated way, suggestive of a functional motor synergy. Lesion and stimulation experiments identified a small region in the rostral anterior interposed nucleus that is necessary and sufficient for the predictive synergistic movements. Neurons recorded within this critical region showed sensorimotor receptive fields with mixed selectivity for multiple body surfaces, providing a neural substrate for the syn-

ergy. An action map for predictive movements within the cerebellum may simplify motor control by reducing the dimensionality of the controlled movements. - NIH NS104836, NIH MH093727

**Herbst MR, Anochili V, Theodore BB, Gilmartin MR**, Marquette University. *Cued fear discrimination in the stress-enhanced fear learning model of post-traumatic stress disorder.*
Dysregulated fear responses following trauma exposure are among the hallmark clinical presentations of post-traumatic stress disorder (PTSD): exaggerated fear to signals of threat, generalized fear to non-threatening situations, and a reduced ability to flexibly control fear responses in the presence of safety signals. Animal models that effectively capture this array of PTSD symptomology are invaluable to making further progress on the neurobiology of pathological fear. One such model is stress-enhanced fear learning (SEFL), which uses an acute stressor followed by mild fear conditioning to trigger traumatic-like memories in rodents. Previous work by Fanselow and colleagues has shown that the enhanced fear to contextual cues produced by SEFL is exaggerated, long-lasting, and resistant to extinction compared with unstressed control rats. In this way, SEFL models key symptoms of PTSD. However, relatively little work using this model has examined the effect of SEFL on fear generalization, particularly to cues. In this study, we tested the hypothesis that stress-enhanced cued fear would show greater generalized fear to a safe cue and a delayed generalization decrement during subsequent discrimination training. Rats received 0 (unstressed controls), 1, or 15 footshocks (1 s, 1 mA) during the stressor phase on day 1 (n = 10/group). All rats then received a single pairing of a white noise conditional stimulus (CS+) and 0.5-mA footshock unconditional stimulus (UCS) on day 2. When tested for fear to the CS the following day, shock-exposed rats showed enhanced cued fear compared with controls, consistent with previous reports. Stressed rats did exhibit elevated fear to a novel tone, but not significantly different from controls. Rats were then trained to discriminate the previously paired CS+ with the tone CS-. Training, which consisted of 15 reinforced CS+ and 15 nonreinforced CS- trials per day, presented pseudorandomly, was conducted over 5 days. The results showed that SEFL rats showed took longer to discriminate between the CS+ and CS- compared with controls, which may arise in part from exaggerated fear to the CS- early in training. These findings suggest that with further optimization, stress-enhancement of cued fear in rodents can also be used to model fear generalization associated with PTSD.

**Heroux, N. A., Miller, L. A., Horgan, C. J., Rosen, J. B., Stanton, M. E.**, Department of Psychological and Brain Sciences, University of Delaware. *Inactivation of the medial prefrontal cortex disrupts immediate early gene expression in the ventral midline thalamus and ventral hippocampus during context memory formation*
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 dissociated into three distinct phases. Both the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHPC) are required for the acquisition and/or consolidation of a context representation during context preexposure in the CPFE in adolescent rats (Heroux et al., 2017; Robinson-Drummer et al., 2016). Moreover, context preexposure induces the expression of the activity- and plasticity-associated immediate early genes (IEGs) c-Fos, Arc, Egr-1, and Npas4 in the mPFC and dHPC (Heroux et al., 2018). The purpose of the current study was to examine whether prefrontal inactivation during context learning impairs the CPFE by interfering with hippocampal or other regional activity recruited for forming a conjunctive context representation. Adolescent (postnatal day 31) rats were given intra-prefrontal infusions of the GABAA receptor agonist muscimol or saline prior to context preexposure, and then were sacrificed 30min later and IEG mRNA expression was analyzed from dissected mPFC, dHPC, ventral midline thalamus (VMT), and ventral hippocampus (vHPC) tissue. Consistent with previous results, prefrontal muscimol infusion during context exposure abolished subsequent post-shock and retention test freezing in behaviorally-tested littermates of the sacrificed groups. Interestingly, prefrontal inactivation abolished IEG expression (c-Fos, Arc, Egr-1, and Npas4) in the mPFC, VMT, and vHPC to the level of behaviorally-naÃŕve home-cage controls, but had no effect on dHPC IEG expression. These results suggest that context memory processes on the preexposure day of the CPFE are likely supported by extended prefrontal-hippocampal circuitry not typically emphasized in configural learning and memory. Future experiments will examine the role of activity and plasticity in these regions across the ontogenetic emergence of the CPFE in developing rats. - [Supported by NIH grant F31AA026503 to NAH; UNIDEL grant to MES]

**Heskje JP, Halverson HE, Jyotis AK, Williams RM, & Parker KL**, Iowa Neuroscience Institute, Department of Psychiatry, University of Iowa. *Pharmacological manipulation of the rat cerebellar cortex at crus I disrupts performance in an interval timing task*
The cerebellum is a key cognitive region in the brain and recent work indicates that cerebellar stimulation may be therapeutic for cognitive dysfunction in disease. While effective, how cerebellar stimulation modifies cerebellar circuits to influence cognition remains unknown. Cognition can be investigated in rodents using timing tasks that require executive processes such as attention and planning. Our previous work indicates that inactivating the lateral cerebellar nuclei (LCN) with GABA agonist muscimol, impairs performance on an interval timing tasks where rodents make a motor indication to estimate the elapse of a temporal interval. To further probe the cerebellar role in this task and to understand how cerebellar transcranial magnetic stimulation which targets the cerebellar cortex and is unlikely to reach deeper structures like the nuclei, we infused a retrograde tracer into the LCN to identify regions of the cerebellar cortex that project there. In congruence with previous primate work, our results indicate that Crus I in the cerebellar cortex is densely connected to the LCN. To probe the role of Crus I in suprasecond time estimation, GABA agonist muscimol (0.5ul, 1 mg/ml) was infused into the right Crus I in 6 rats trained in the interval timing task. We report that time estimation was significantly disrupted indicating a role for Crus I in cognitive processes. GABA antagonist GABAzine, (0.5ul, 0.0002mg/ml) was also infused as an approach to stimulate Crus I and this manipulation did not have any effect on timing performance. Work is currently underway to pair these manipulations with Purkinje Cell recordings to further understand how cerebellar stimulation may influence cerebellar function

and if stimulating Crus I may influence cognition in rodents that have frontal cortex dysfunction and timing impairments. This work supports a role for Crus I in the cerebellar cortex in cognitive function and may provide evidence for how cerebellar stimulation can improve cognition.

**Heslin KH, De Corte BJ, Parker KL**, University of Iowa . *Dissociating effects of pharmacological manipulation in the lateral cerebellar nuclei: interval timing or cue discrimination deficit?*
Interval timing, or timing in the seconds to minutes range, depends on an extended network of brain regions. Cerebellar involvement in interval timing circuitry in the supra-second range has been a point of disagreement. Some studies in humans and animals have specifically suggested that the lateral cerebellar nuclei (dentate nuclei in humans) may be necessary for performing a range of interval timing tasks. Our lab has used pharmacological manipulation of the lateral cerebellar nuclei during a dual duration fixed interval timing task to probe this topic in rats. Notably, focal delivery of the GABA agonist muscimol and the D1 dopamine receptor antagonist SCH23390 to the lateral cerebellar nuclei appears to impair performance in 12 second, but not 3 second fixed interval trials. However, due to the task structure used, it is ambiguous whether these results were due to a true interval timing deficit, or an alternative impairment such as decreased ability to discriminate between the 3 second and 12 second trial cues. Therefore, three follow-up experiments were employed to interpret these past results. The first two experiments probed interval timing ability during lateral cerebellar nuclei inactivation without the possibility of cue conflict. The third follow-up experiment uses a modified version of the original dual duration fixed interval task but provides information about perceived trial type. Preliminary data suggest possible cue discrimination impairment rather than interval timing disruption with muscimol and SCH23390 infusion in the lateral cerebellar nuclei.

**Hilz, E, N., Smith, R. W., Monfils, M. H., & Lee, H. J.**, The University of Texas at Austin. *Mapping the estrous cycle to context-specific extinction memory*
In Pavlovian conditioning, context can gain predictive value over learned associations. The gonadal hormone estradiol has been shown to increase synaptic plasticity in areas of the brain known to play an important role in both context information processing and memory retrieval of conditioned behavior; however, little research has examined if natural fluctuations in estradiol across the estrous cycle modulate the expression of contextual learning and memory. Here we examine the influence of the estrous cycle on renewal of appetitive behavior utilizing an ABBA paradigm. We establish that rats in the proestrus stage during extinction training exhibit elevated renewal behavior compared to rats in either metestrus or diestrus. Only rats in proestrus during extinction training (but not during the renewal test) exhibited elevated renewal behavior , which suggests that the estrous cycle may influence renewal in a state-dependent fashion. After context renewal, rats were euthanized and brain processed for immunohistochemistry. We examined fos induction within the prelimbic and infralimbic areas of the medial prefrontal cortex, the dorsal and ventral hippocampal formation, the paraventricular nucleus of the thalamus, and areas of the amygdala. In each area, we found differential fos induction which corresponded to the behavioral differences observed between groups. Results from this study suggest that context information processing may vary as a function of endogenous female hormones across the gonadal hormone cycle, and that encoding and retrieval of this information is accomplished in a state-specific manner.

**Hoffman AN, Hsieh E, Pennington ZT, Watson S, Hovda DA, Giza CC, Fanselow MS**, UCLA Neurosurgery; Brain Injury Research Center; UCLA Psychology; UCLA Steve Tisch BrainSPORT Program; UCLA Medical and Molecular Pharmacology; Mattel Children's Hospital UCLA; UCLA Psychiatry & Biobehavioral Sciences; Staglin Center for Brain and Behavioral Health. *Projection specific mechanisms of auditory sensitivity that contribute to enhanced fear after TBI*
Traumatic brain injury (TBI) increases the risk for post traumatic stress disorder (PTSD), however the underlying neurobiology of this comorbidity is unknown. Sensory sensitivity is common following TBI, and changes in sensory processing might influence the encoding of traumatic events in the wake of injury. The lateral amygdala (LA) receives direct sensory cortical and thalamic inputs necessary for the formation of auditory fear memories, and may be vulnerable to TBI. We have shown enhanced contextual fear after lateral fluid percussion injury (FPI) in rats following fear conditioning when white noise, but not when low frequency tones signal mild aversive footshocks. Altered sensitivity to white noise might reflect phonophobia after FPI and underlie increased fear after injury when used in fear conditioning. We hypothesized that FPI enhances contextual fear to white noise-signaled conditioning due to altered sensory-emotional network processing. In this study we show that when rats are exposed to 75dB white noise alone prior to fear conditioning, FPI rats demonstrate robust defensive behavior and show increased context fear after white noise-signaled fear conditioning relative to sham. We also show increased neuronal activity within the ipsilateral LA in FPI rats during white noise exposure relative to noise-exposed shams and quiet FPI controls with Arc immunohistochemistry. Finally, to determine functional activity in sensory projections to LA, we bilaterally infused retrograde tracer cholera toxin B (CTB) three weeks before FPI and measured c-Fos expression in CTB+ cells during white noise exposure. In this experiment we demonstrate that the increased activity in the ipsilateral LA is driven by increased activity in neurons projecting from ipsilateral auditory thalamus (medial geniculate nucleus, MGN) to LA as measured by more c-Fos in CTB+ MGN neurons during white noise exposure. This effect was specific to the MGN and not secondary auditory cortex (Te3)-LA projections, indicating the specificity of the inputs that drive increased plasticity and corresponding defensive behavior. These data provide implications for the vulnerability of the thalamo-amygdala pathway underlying phonophobia and altered sensory processing after TBI, where otherwise neutral stimuli may adopt aversive properties and impact encoding of traumatic memories contributing to psychiatric comorbidities. - F32NS098694: AH; R01MH062122: MSF; UCLA Depression Grand Challenge Fellowship Fund: MSF; UCLA Brain Injury Research Center; 1PO1NS058489: DH, CG; 1R01NS27544: DH, CG; Centre for NeuroSkills: DH; UCLA Steve Tisch BrainSPORT: CG; Easton Labs for Brain Health; Staglin Center for Brain and Behavioral Health.

**Horenstein K, Chowdhury A, Lipatova O, Campolattaro MM**, Christopher Newport University. *Transfer of Associative Responding Between Off and On Cues*

The present experiment was designed to examine how quickly rats transfer learning between "cue-off" and "cue-on" conditioned stimuli (CSs). All rats were first trained using eyeblink conditioning procedures to associate the absence of a background tone (i.e., a tone-off CS) with periorbital electrical stimulation. This training produced high levels of conditioned eyeblink responses. Rats were then given additional training sessions, but the cue was switched to either a tone-on, light-on or light-off CS. We found that the rate of conditioning to the tone-on and light-on CSs occurred more rapidly than initial acquisition to the tone-off CS, which confirms that rats can quickly transfer associative responding between "off" and "on" CSs. However, no facilitated transfer was observed in rats that were switched to the light-off CS. It is possible that altering the appearance of the experimental context (i.e., from a dark to illuminated environment) muted the facilitated transfer effect. Thus, we hypothesize that discrete and contextual cues can sometimes compete for associative strength during transfer training.

**Hunsberger, HC, Scarlata, M, Jayaseelan, K, & Denny, CA**, Columbia University/ New York State Psychiatric Institute. *Anxiety Predicts Cognitive Decline in a Sex-Specific Manner in Alzheimer's Disease Mice*

BACKGROUND: Alzheimer's disease (AD), a progressive and debilitating neurodegenerative disorder, stands alone as one of the ten leading causes of death in the United States that cannot be prevented, slowed, or cured. Interestingly, psychiatric disturbances, such as depression and anxiety are observed in 90% of AD patients and these symptoms usually manifest long before AD onset. Although much of the field has focused on the link between depression and AD, recent clinical evidence supports that anxiety can predict the progression to AD above and beyond depression, brain atrophy, and cognitive impairment. Moreover, although most AD studies have been performed using male mice, recent evidence suggests that females are more susceptible to depression, anxiety, and AD when compared to males. METHODS: To gain a mechanistic insight into how anxiety impacts AD progression, we performed a longitudinal study on mood and cognition in female and male AD (APP/PS1) mice. RESULTS: Female AD mice had increased anxiety at an earlier age than male AD mice and their anxiety levels correlated with cognitive decline at a later age. Female AD mice were also impaired in cognition at an earlier age than male AD mice. Neural activity was altered in the hippocampus of AD mice. CONCLUSIONS: Our data indicate that there is a relationship between anxiety and AD progression, and thus, could provide crucial insights into the mechanisms underlying cognitive decline at a vital therapeutic time window. - T32 MH015174-40 (NIH) Translational Neuroscience Training Grant The purpose of this program, which is entering its 40th year, is to train postdoctoral fellows to do research on a variety of neuroscience topics relevant to psychiatric disorders. Role: Postdoctoral fellow

**Josselyn SA**, Hospital for Sick Children (SickKids), University of Toronto. *Making memories*

A fundamental goal of neuroscience is to understand how information is encoded and stored in the brain. The physical or functional representation of a memory (the memory trace or "engram") is thought to be sparsely encoded over a distributed memory network. However, identifying the precise neurons which make up a memory trace has challenged for scientists since Karl Lashley's "search for the engram" in the 1950's (Josselyn, 2015; Lashley, 1950; Josselyn, 2010; Josselyn et al., 2015). Moreover, it was not known why one neuron (rather than its neighbour) was involved in a given memory trace. We previously showed that lateral amygdala (LA) neurons with increased levels of the transcription factor CREB (cAMP/Ca++ Responsive Element Binding protein), are preferentially activated by fear memory expression, suggesting they are selectively recruited into the memory trace (Han et al., 2007). We, and others, went on to show that these neurons were critical components of the memory network by selectively ablating (Han et al., 2009) or inactivating them (Zhou et al., 2009). These findings established a causal link between a specific neuronal subpopulation and memory expression, thereby identifying critical neurons within the memory trace. Furthermore, these results suggest that at least within the LA, eligible neurons compete for inclusion in a memory trace, and that the winners of this competition are determined by relative CREB function. Although competition between neurons, axons and synapses is necessary for refining neural circuits in development, little is known about competition between neurons in the adult brain. Our recent results suggest that this neuronal competition during memory formation limits the overall size of the memory trace (number of "winning" neurons) and is a mechanism that links (or disambiguates) related memories in the LA (Rashid, et al., 2016). Memory impairments are a hallmark of aging, major mental illnesses (e.g., schizophrenia and depression) as well as neurological disorders (e.g., Alzheimer's and Parkinson's diseases). Therefore, understanding how the brain encodes and stores information is highly relevant to both mental health and mental illness.

**Kim J, Broschard MB, Castro L, Wasserman EA, Freeman JH**, Dept of Psychological Brain Sciences, UIowa. *Roles of medial prefrontal cortex in rodent visual categorization*

The current study explored how category-feature density affects visual category learning, retrieval, and generalization to the visually altered stimuli. Using a touchscreen apparatus, rats were trained to categorize multiple abstract stimuli into two different categories. The abstract stimulus was a pentagonal configuration of five visually distinctive features. Some of the features were relevant for defining the category but the others were irrelevant. Rats were assigned to two groups, high or low category-feature density. Upon learning to criterion, cannulae were implanted bilaterally in the medial prefrontal cortex (mPFC). After recovery, rats were given either PBS or muscimol into the mPFC before different testing sessions. They were tested with the trained stimuli for retrieval as well as with novel and visually altered stimuli for generalization. The results showed that rats differed in learning visual categorization task by category-feature density; high density rats reached criterion significantly quicker than low density rats. In testing, muscimol inactivation of the mPFC impaired retrieval of the trained stimuli and generalization to the novel stimuli in both feature-density groups. The results demonstrated that rat visual categorization is critically dependent upon intact mPFC function.

**Kirry AJ, Twining RC, Gilmartin MR**, Marquette University, Milwaukee, WI. *Prelimbic input to the basolateral amygdala is needed early in the acquisition of trace fear conditioning.*
The association of a neutral conditional stimulus (CS) and an aversive footshock unconditional stimulus (UCS) in fear conditioning critically depends on the amygdala. However, if the CS and UCS are separated by several seconds as in trace fear conditioning, additional brain areas are needed, including the prelimbic area (PL) of the medial prefrontal cortex. Our previous work showed that a subset of PL cells exhibit sustained firing in response to and which outlasts the CS, and that prefrontal activity during the trace interval between the cue and shock is necessary for cued learning. The PL may thus provide a bridging signal to link the CS and UCS in memory, but it is unclear if such a signal is directly integrated in the basolateral amygdala (BLA) to support fear learning. In a series of experiments using pathway-specific optogenetic and chemogenetic manipulation of PL to BLA communication in rats during trace fear conditioning, we tested the hypothesis that direct input to the BLA from PL is necessary for the formation of a trace fear memory. First, we found that neither optogenetic silencing nor stimulation of PL terminals in the BLA during the trace interval on each of 6 paired trials impaired memory formation. Stimulation did however drive the expression of fear during extinction acquisition and recall. The null effects on fear learning were corroborated using intersectional chemogenetics to silence the PL-BLA pathway during the entire acquisition session. These results suggest that direct communication between the PL and BLA during the acquisition session is dispensable for trace fear conditioning. However, two follow-up analyses point to a potential function for this direct pathway. First, in the optogenetic experiments, fiber placement within the BLA correlated with cued fear at test, which along with a rostral-caudal gradient of immunohistochemical expression of amygdala Arc after PL silencing, raises the possibility that PL input to the anterior, but not posterior, BLA is needed for trace conditioning. Second, in an experiment in which animals were given only two trials of trace conditioning per day for 3 days, chemogenetic silencing of the PL-BLA connection impaired learning. Together, these results suggest that direct input to the BLA from the PL may be dispensable for cued fear learning over the course of several trials, but this connection, particularly to the anterior BLA, may facilitate acquisition early in training when the CS-UCS relationship is most uncertain.

**Kitamura T**, University of Texas Southwestern Medical Center. *Neural circuits for the regulation of trace fear conditioning*
We have previously identified that pOxr1+ excitatory cells in the medical entorhinal cortex layer III (MECIII cells) project to the hippocampal CA1 pyramidal cells and are crucial for the trace fear conditioning (TFC). On the other hand, CalB+ excitatory cells in MECII (CalB+ cells) project to the GABAergic neurons in the hippocampal CA1, suppress the MECIII input into the CA1 pyramidal cells through the feed-forward inhibition, and inhibit TFC. These findings lead us to propose a novel model that successful TFC depends on the neural activity balance between pOxr1+ and CalB+ cells in the MEC. To test this hypothesis, we examine Pavlovian trace fear conditioning combined with transgenic mice strategy, in vivo calcium imaging, viral tracing of neural circuits, optogenetic manipulation and gene manipulation in all cell-type specific manner.

**Knowlton, B.J., Patterson, T.K.**, Dept. of Psychology, UCLA. *Reduced sensitivity to devaluation after early-life stress*
Early-life stress is associated with a number of negative health outcomes, including increased rates of addiction, alcoholism, and obesity, during adulthood. For each of these conditions, what are initially goal-directed actions are thought to become habitual, leading to a pathological loss of control over behavior. We are exploring the idea that early-life stress leads to developmental changes in the brain that facilitate the transition from action to habit during instrumental learning. In the studies I will describe, we collected retrospective self-report data on adverse early life experiences (e.g. loss of parent, physical abuse) from healthy undergraduates using standardized questionnaires. We then compared those reporting early life stress with those that did not on instrumental learning procedures. Using an appetitive procedure, we found that people reporting early life stress showed a reduced partial reinforcement extinction effect compared to those who did not. In an avoidance procedure, we also showed that early life stress was associated with continued responding after outcome devaluation. These initial results suggest that early-life stress, even in otherwise healthy individuals, may alter the trajectory of instrumental learning that may contribute to health risk later in life. - NIH-NIDA 1R01DA045716-01

**Kwapis JL, Alagbhand Y, KramÃąr EA, LÃşpez AJ, Vogel Ciernia A, White AO, Shu G, Rhee D, Michael CM, Montellier E, Liu Y, Magnan CN, Sassone-Corsi P, Baldi P, Matheos DP, Wood MA**, University of California, Irvine. *Epigenetic regulation of the circadian gene Per1 contributes to age-related impairments in long-term memory*
Aging is accompanied by impairments in both long-term memory and circadian rhythmicity. Although it is clear that memory is affected by circadian cycling, it is unknown whether age-related disruption of the circadian clock causes impaired hippocampal memory or whether these biological processes simply share a common mechanism that is altered with age. Here, we tested whether dysregulation of a key epigenetic mechanism, histone deacetylase 3 (HDAC3) in the aging hippocampus might contribute to impairments in long-term memory formation. HDAC3 typically represses gene expression by removing acetyl groups from histone tails and has previously been shown to be a key negative regulator of long-term memory formation. We hypothesized that dysregulation of HDAC3 activity in the aging brain contributes to an unusually repressive chromatin structure that limits synaptic plasticity and memory formation. To test this, we disrupted HDAC3 in the dorsal hippocampus of 18-month-old mice with two different manipulations: focal genetic deletion with HDAC3flox/flox mice and activity-specific disruption with a dominant-negative point mutant virus (AAV-HDAC3(Y298H)). We found that deletion or disruption of HDAC3 ameliorated age-related impairments in both long-term memory and synaptic plasticity. To identify the mechanism through which HDAC3 deletion ameliorates age-related memory impairments, we ran RNA sequencing on hippocampal tissue from young mice, aging mice, and aging mice with focal HDAC3 deletion in the dorsal hippocampus. We identified a subset of genes, including the circadian gene Period1 (Per1), that is restricted in the aging hippocampus by HDAC3. Using siRNA-mediated knock-

down of PER1 protein, we show that hippocampal PER1 is critical for long-term memory formation in young mice. Finally, to determine whether overexpression of Per1 is sufficient to ameliorate age-related memory impairments, we locally upregulated Per1 in the dorsal hippocampus using two methods: lentivirus-mediated overexpression of wildtype Per1 (pLVX-Per1) or transcriptional activation of Per1 using the CRISPR/dCas9 SAM system. Both methods demonstrate that overexpression of Per1 in the dorsal hippocampus can ameliorate age-related impairments in long-term memory formation. Together, our data suggest that HDAC3-mediated repression of Per1 contributes to age-related impairments in long-term memory formation. More broadly, this age-related disruption of Per1 might connect age-related impairments in both long-term memory and circadian rhythmicity, depending on the structure.

**Lafferty DS, Petrovich GD**, Psychology, Boston College. *The effect of context familiarity on context-induced appetitive renewal in male and female rats*

The environments in which we consume food can later influence eating behavior. Food cues from the environment can stimulate food seeking, but how we respond depends on context. Context-mediated renewal is a well-suited paradigm to investigate environmental control of responding to food cues. Recent work found that males demonstrate robust context-mediated renewal of responding to a food cue after extinction but females do not. These results were established in rats with an "ABA" paradigm in which a cue-food association is acquired in one context, extinction of the conditioned responding occurs in a different context, and the renewal of responding is induced by the acquisition context. The goal of the current study was to determine if this renewal effect could be strengthened, particularly in females, by pre-exposure to both contexts prior to training. First, food restricted adult male and female rats were habituated to the training contexts (experimental groups) or remained in their homecage (control groups). Then all rats underwent Pavlovian conditioning in which they were presented with a tone cue (conditioned stimulus, CS) followed by delivery of palatable food pellets (unconditioned stimulus, US). Acquisition of the CS-US association occurred in a distinct context that varied in olfactory, visual, and tactile features from the context used for extinction training. By the end of acquisition training (5 sessions, each with 8 CS-US pairings) all groups showed similar robust conditioned responding (approach to the foodcup) during the CS. After extinction training (2 sessions, each with 8 CSs) all groups decreased responding during the CS. Rats were tested for renewal of responding with CS-only presentations in each context, on separate days counterbalanced for order. Here we compared responding during the CS (elevation above baseline) in the acquisition vs. extinction contexts. Initial experiments included US delivery during pre-exposure, and the current experiment omitted US delivery. Pre-exposure with US delivery did not improve renewal of responding in either sex. Analyses for the present experiment revealed robust renewal in males that received pre-exposure, as indicated by their higher responding during CSs when tested in the acquisition compared to extinction contexts ($t(1,5)=7.55$, $p<.01$). The females that received pre-exposure also showed higher responding during CSs upon testing in the acquisition compared to extinction contexts, but this effect did not reach significance ($t(1,6)=2.20$, $p=.07$). Current results suggest that pre-exposure to the training contexts may strengthen the renewal effect in males, and may be able to help induce renewal in females. Preliminary results suggest that the effects of context pre-exposure on renewal of responding in this protocol depend on whether US was delivered during the pre-exposure sessions. - Research was supported by NIH, NIDDK Grant R01DK085721

**LaLumiere RT**, University of Iowa. *Amygdala influences on memory consolidation: Insights from multiple memory systems*

Although much evidence indicates the basolateral complex of the amygdala (BLA) influences the consolidation for many different kinds of memories, the circuitry mechanisms underlying this modulatory influence have not been clear. In fact, whereas the BLA modulates the consolidation for memories as diverse as spatial and cued-response water maze, conditioned taste aversion, and inhibitory avoidance, other brain regions play more selective roles. In recent years, our work has begun to tease apart the circuits by which the BLA engages in memory modulation and suggests that different efferent projections influence only specific aspects or types of memories. Using optogenetic approaches, our evidence indicates that the BLA projections to the ventral hippocampus selectively influence the consolidation of the emotional, footshock-based component for contextual fear conditioning. In contrast, BLA projections to the medial entorhinal cortex modulate the consolidation of contextual and spatial memories, as assessed with both contextual fear conditioning and Barnes maze-based tasks. Additionally, our findings indicate that stimulating the BLA afferents to the medial entorhinal cortex following training for a cued-response task in the Barnes maze impaired retention, in agreement with the hypothesis that spatial and cued-response learning use different neural systems that compete with one another. Moreover, across our studies, the findings suggest that only specific frequencies of stimulation are effective in enhancing memory. Whereas stimulating BLA afferents to the ventral hippocampus with bursts of 40 Hz stimulation enhances the consolidation of the footshock-based memories, stimulating BLA afferents to the medial entorhinal cortex is only effective at enhancing spatial memories and impairing cued-response memories when using bursts of 8 Hz stimulation.

**Lattal M**, Oregon Health & Science University. *Epigenetic modulation of deficits in trace fear conditioning following withdrawal from chronic cocaine*

Interactions between abused substances and fear conditioning are well documented, with demonstrations that fear conditioning can have lasting effects on drug-seeking and that acute exposure to drugs of abuse can alter acquisition and expression of conditioned freezing. Further, many studies have found that binge exposure to psychostimulants causes cognitive impairments in humans and rodents, particularly in tasks that require prefrontal cortex function. We used trace fear conditioning as a tool to study the effects of withdrawal from cocaine on cognitive function in rats and mice. In this talk, I will review findings showing that (1) trace fear conditioning can be positively and negatively modulated by drugs that target histone acetylation in the medial prefrontal cortex; (2) passive exposure to repeated injections of cocaine in mice or active exposure to intravenous self administration of cocaine in rats leads to selective deficits in trace fear conditioning; (3) these deficits occur soon or long after drug exposure and are correlated with reduced

histone acetylation in the prelimbic cortex; and (4) deficits can be reversed by systemic or site-specific delivery of a histone deacetylase inhibitor. Together, these experiments show the utility of trace fear conditioning for revealing withdrawal-associated cognitive impairments and suggest that modulation of histone acetylation may serve as a useful target for reversing these deficits. - NIDA, NIMH, Department of Defense

**Laughlin L[1,2], Sears R[1,2], Campese V[3], Cain C[1,2]**, [1]NYU School of Medicine, Department of Child & Adolescent Psychiatry, New York, NY 10016, [2]Nathan Kline Institute for Psychiatric Research, Emotional Brain Institute, Orangeburg, NY, 10962, [3]University of Evansville, Departments of Psychology and Neuroscience, Evansville, IN, 47722. *Role of dorsolateral striatum in habitual active avoidance responding*

In instrumental tasks with appetitive outcomes, dorsomedial striatum (DMS) mediates outcome-dependent responding and dorsolateral striatum (DLS) mediates habitual responding. However, the psychological and neural mechanisms of aversively-motivated instrumental behavior, like signaled active avoidance (SigAA), are poorly understood. In a typical SigAA procedure, a warning signal (WS) predicts a painful unconditioned stimulus (US; e.g. footshock) and subjects can terminate the WS, prevent the US and produce safety stimuli by emitting a predetermined avoidance response (AR; e.g. shuttling). We devised a novel outcome-devaluation procedure to test the role of safety signals and the dorsal striatum in rodent AR performance. The standard SigAA procedure was modified to include explicit feedback stimuli (FB) that immediately followed each successful AR, thus transforming the FB into a conditioned inhibitor (safety signal). We performed outcome-devaluation in separate chambers by pairing FB with footshocks. Final tests occurred back in the avoidance context where WSs were repeatedly presented in extinction. FB-devaluation impaired ARs after 5, but not 20 days of training (compared to unpaired controls that still valued the FB). In separate rats trained for 20 days, we next tested whether FB-devaluation affects AR performance with DLS activity suppressed (via kappa-opioid receptor DREADD (KORD)-mediated inhibition). Activation of KORD receptors in DLS with the biologically inert ligand Salvinorin B (2 mg/kg, i.v.) impaired ARs in rats subjected to FB-devaluation; ARs remained high in FB-valued and vehicle control groups. Together these data suggest that 1) FB safety signals are an important outcome in AR acquisition, 2) overtraining causes a shift from outcome-dependent to habitual avoidance, and 3) DLS mediates habitual AR performance, similar to its role in appetitive instrumental habits. Studies of DMS are ongoing, however, preliminary data strongly indicate that DMS is required for moderately-trained (i.e. outcome-dependent) ARs. - R01 MH114931 to CKC

**Lebonville CL, Wangler LM, Jones ME, Paniccia JE, Parekh SV, Fuchs RA, Lysle DT**, Psychology and Neuroscience, UNC-Chapel Hill; Integrative Physiology and Neuroscience, Washington State University. *Role of hippocampal outputs in context-heroin conditioned immune modulation*

Through Pavlovian conditioning, exposure to opioid-associated environments, like opioids themselves, can produce peripheral immune system changes. Functional integrity of the dorsal hippocampus (DH) is required for conditioned immune modulation, yet the required downstream hippocampal targets have yet to be determined. It is also not known whether the ventral hippocampus (VH) or its downstream targets are required for heroin conditioned immune modulation. To begin to understand more about the role of the hippocampus at the circuit level, the current studies employ designer receptors exclusively activated by designer drugs (DREADD) to inhibit either dorsal or ventral subiculum (dSub or vSub), two major hippocampal output regions. In this paradigm, a contextual conditioned stimulus (CS) is paired with a heroin unconditioned stimulus (US) for five, 1-h sessions. Subsequent exposure to the CS results in suppression of lipopolysaccharide (LPS)-induced measures of nitric oxide (NO), an important immune regulator. We bilaterally infused an adeno-associated viral vector containing a Gi-coupled DREADD construct (AAV5-CAMKIIÎś-hM4D(Gi)-mCherry) into either the dSub or vSub of male rats. Six days after the last conditioning day, rats received systemic injections of either the DREADD agonist, clozapine-N-oxide (CNO; 3 mg/kg), or vehicle. Thirty minutes later, rats were exposed to the heroin-paired context for 1 h or remained in their home cages as a control. Immediately after CS exposure or home cage stay, rats received a systemic injection of LPS (1 mg/kg) to elicit a pro-inflammatory response, including NO production. Six hours later, spleen tissue was collected to assess NO production. Chemogenetic inhibition of the dSub, but not the vSub, disrupted the ability of the CS to suppress LPS-induced NO production. These findings provide rationale for investigating the contribution of DH afferent connections in heroin conditioned immune modulation with future studies. - This work was funded by the National Institute on Drug Abuse (DA034721, DA007244) and the National Science Foundation (DGE-1144081).

**Lensing A, Pajser A, Fisher H, Boerger R, Gilbert S, Lin H, Pickens C**, Kansas State University. *The relationship of adolescent/early adult alcohol consumption and instrumental extinction learning*

We previously found that, in Long-Evans rats given chronic intermittent access (CIA) to alcohol during adolescence/early adulthood, rats that consumed high levels of alcohol also exhibit faster instrumental extinction during a devaluation test. Here, we determined whether alcohol consumption would correlate with instrumental extinction without a concurrent devaluation manipulation. Rats received CIA (n=21) or water-only (n=15) access for 6 weeks (PND 26-66). Ten days after completion of the CIA paradigm, rats began behavioral training. Once free-operant lever pressing was established, the rats received 2 once-daily sessions of cued instrumental training. Finally, the rats underwent extinction training. We found that rats given previous alcohol access exhibited faster instrumental extinction. We also found a correlation of higher drinking alcohol rats exhibiting a faster rate of extinction. Our data suggest that alcohol consumption can alter the instrumental extinction rate. Future research will be needed to determine the neurobiological basis of this relationship, and also whether the alcohol-extinction correlation represents a dose-dependent neurotoxic effect or represents an individual differences relationship that co-exists with the neurotoxic effect.

**Li A, Kirunda A, Miller L, Wasielewski S, Golden E, Fanikos M, Trettel, S Shansky RM**, Northeastern University. *Tipping the scales: situational modulators of active vs. passive conditioned fear responses*

Classical Pavlovian fear conditioning has been widely used to study stress learning mechanisms. An animal's level of fear is typically evaluated by "freezing", but recent studies have identified a wide array of behaviors, suggesting that freezing is an incomplete measure of fear. Our previous work identified and characterized "darting", a sexually dimorphic active fear response predictive of improved extinction retention. However, darting is not observed in all animals, and here we investigated situational factors–including prior stress exposure, intensity of the unconditioned stimulus (footshock), and chamber size–that may increase or decrease the size of darting subpopulations within male and female cohorts.

**Lingg RT, Johnson SB, Emmons EB, Anderson RM, Romig-Martin SA, Narayanan NS, LaLumiere RT, Radley JJ**, University of Iowa. *Evidence for the involvement of the bed nucleus of the stria terminalis in memory consolidation*

Memory consolidation following stressful experiences is a key means of adaptation, allowing an individual to create a long-term representation of the event, and thereby evaluate the severity of future threats of the same or similar kind. It is well documented that the consolidation process is enhanced by glucocorticoids, the end-products of the HPA cascade, via activation of cognate receptors in the basolateral amygdala. Both systemic and intra-amygdaloid administration of corticosterone or glucocorticoid receptor agonists following training have been shown to enhance later retention. Nevertheless, there remain lingering questions concerning what changes in endogenous glucocorticoid activity are necessary to enhance memory, which neural systems are involved in this modulation, and whether they overlap with the neural systems more directly implicated in memory encoding. Previous work from our laboratory has established an important role for the anteroventral subdivision of the bed nuclei of the stria terminalis (avBST) in the modulation of the HPA axis. Moreover, avBST maintains extensive connectivity with a network of limbic cortical circuitry canonically associated with memory consolidation. As such, avBST is well positioned to act within the traditional framework of the consolidation network and as a regulatory locus for the hormonal modulation of memory strength. Here we used an optogenetic approach to manipulate activity within avBST and downstream pathways to examine its role during memory consolidation using a single trial inhibitory avoidance learning task. First, we showed that 10-minute post-training optogenetic manipulations of avBST somata bi-directionally modulated retention when rats were tested two days later. Specifically, photoinhibition with Archaerhodopsin and photoexcitation with Channelrhodopsin led to a two-fold enhancement and decreased retention (by 45%, $p < 0.05$ for each), respectively. Follow-up experiments revealed that GABAergic projections from avBST to the paraventricular hypothalamus were largely responsible for increased retention latencies (by 200%, $p < 0.05$) following post-training photoinhibition of halorhodopsin-expressing avBST axonal fibers in PVH. As our results suggested that this effect was contingent upon an elevated stress responsiveness of pituitary-adrenal output, in an additional study rats were pre-treated with a glucocorticoid synthesis inhibitor (11-beta-hydroxylase, 50mg/kg s.c.) prior to inhibitory avoidance training and post-training photoinhibition of avBST. We found that blockade of training-induced HPA activation precluded the memory enhancing effects of avBST inhibition. An additional series of experiments identified post-training photoexcitation of avBST terminal fibers in PVH was unable to attenuate either HPA responsiveness or consolidation, indicating separable processes by which the bi-directional coordination of consolidation occurred. Further investigation revealed that avBST GABAergic innervation of the ventrolateral periaqueductal gray (vlPAG) provided the downstream basis for the attenuation of consolidation. Specifically, post-training photoexcitation of avBST Channelrhodopsin expressing fibers in vlPAG was sufficient to reduce retention 48hrs later (by 53%, $p < 0.05$), an effect that was independent of changes in HPA reactivity. Together, these data support a role for separable avBST processes in the modulation of memory consolidation, whereby biasing avBST activity toward excitation or inhibition engages the capacity to restrict or augment consolidation, respectively.

**Malvaez M, Shieh C, Murphy MD, Greenfield VY, Wassum KM**, Dept. of Psychology, UCLA, Los Angeles, CA 90095. *Distinct cortical-amygdala projections drive reward value encoding and retrieval*

The value of an anticipated rewarding event is crucial information in the decision to engage in its pursuit. The networks responsible for encoding and retrieving this value are largely unknown. Using glutamate biosensors and pharmacological manipulations, we found that basolateral amygdala (BLA) glutamatergic activity tracks and mediates both the encoding and retrieval of the state-dependent incentive value of a palatable food reward. Projection-specific chemogenetic and optogenetic manipulations revealed the orbitofrontal cortex (OFC) supports the BLA in these processes. Critically, the function of lateral (lOFC) and medial (mOFC) OFC to BLA projections was found to be doubly dissociable for value encoding and retrieval, respectively. These data reveal a new circuit for adaptive reward valuation and pursuit, indicate dissociability in the encoding and retrieval of reward memories, and provide insight into the dysfunction in these processes that characterizes myriad psychiatric diseases. Ongoing experiments are evaluating the BLA efferent pathways required for value-based decision making.

**Manzano Nieves G, Johnsen A, Bravo M, Bath KG**, Brown University. *Early life stress is associated with precocious amygdala development but delayed prefrontal development*

Early life stress (ELS) is associated with an increased risk for later development of emotional pathology such as depression and anxiety. The origins of pathology are thought to be rooted in atypical development of circuits regulating emotional responding, including the amygdala. Here we used a mouse model of ELS, in the form of maternal bedding restriction, and tested the effect on amygdala development, and the development of freezing behavior in a tone-associated fear conditioning paradigm. Previous work has established that tone-associated freezing develops as early 15 days of age and stays relatively stable across early development. Here, we found that mice reared under ELS conditions show an unexpected and significant decrease in freezing behavior at 21 days of age. This decrease in freezing behavior was associated with a precocious

maturation and increased density and activity of Parvalbumin (PV)-positive cells in the basal amygdala (BA). To test if the spike in PV-cells was related to suppressed freezing behavior, we optogenetics to silence this population of cells in the BA during acquisition and testing phase in the conditioning paradigm. We found that silencing BA PV cell restored normal levels of freezing behavior in ELS reared mice. To understand how medial prefrontal (mPFC) projections may be influencing the fear response we assessed mPFC to BA projection density. We found that ELS delays the emergence of these projections. These results have implications for understanding the effects of ELS on the ontogeny of circuit development and its impact on the development conditioned fear.

**Maren S**, Dept Psychological and Brain Sciences, Texas A&M Univ. *The way forward is backward: BNST mediates fear to ambiguous threats*
The bed nucleus of the stria terminalis (BNST) has been implicated in fear and anxiety, but the specific factors that engage the BNST in defensive behavior are unclear. Here we explore the possibility that ambiguous threats recruit the BNST during Pavlovian fear conditioning in rats. We arranged a conditioned stimulus (CS) to either precede or follow an aversive unconditioned stimulus (US), a procedure that established reliable (forward) or ambiguous (backward) signals for US onset. After conditioning, reversible inactivation of the BNST selectively reduced freezing to the backward CS; BNST inactivation did not affect freezing to the forward CS even when that CS predicted a variable magnitude US. Backward CSs increased Fos in the ventral BNST and in BNST-projecting neurons in the infralimbic cortex, but not the hippocampus or amygdala. These data reveal that BNST circuits process ambiguous threat signals central to the etiology and expression of anxiety. - NIH, McKnight Foundation, Brain & Behavior Research Foundation

**McReynolds JR, Schaps B, Wolf CP, Mathy JC, Hillard CJ, Mantsch JR**, Department of Biomedical Science, Marquette University, Milwaukee WI; Department of Pharmacology & Toxicology and Neuroscience Research Center, Medical College of Wisconsin, Milwaukee, WI. *Role of mesolimbic endocannabinoid signaling in chronic electric footshock stress-induced escalation of cocaine intake in rats*
Stress is an important contributing factor to addiction and is problematic as stress is unavoidable in daily life. Addiction can be characterized by a loss of control over drug intake that is modeled by escalating patterns of drug self-administration (SA). We have previously shown that a stressor, electric footshock stress, administered daily at the time of SA induces an escalation of cocaine intake in rats that would otherwise demonstrate stable cocaine SA under short-access conditions (2-h/day). Stress-induced escalation of SA is likely the consequence of neuroplastic changes that involve neurobiological mediators that connect stress-responsive and reward systems in the brain, such as the endocannabinoid system (eCB). These changes likely occur in regions implicated in both stress and reward, such as the nucleus accumbens shell (NAc) and ventral tegmental area (VTA). We hypothesize that repeated stress at the time of SA induces a persistent increase in eCB signaling, in the NAc shell and VTA, that results in escalation of cocaine use and increased susceptibility to later reinstatement. Male SD rats were trained to SA cocaine (0.5 mg/kg/inf) on a FR 4 schedule in 4 X 30 min SA sessions separated by 5-min drug-free periods. Some rats received shock in the SA chamber during the 5 min drug-free period over 14 days. Systemic administration of the CB1R antagonist AM251 (1 mg/kg) prior to the SA session attenuated cocaine intake only in stress-escalated rats. Intra-NAc shell administration of AM251 (1, 3 $\mu$g) attenuates cocaine intake only in stress-escalated rats. Surprisingly, intra-VTA administration of AM251 (1, 3 $\mu$g) prior to the SA session appears to attenuate intake in non-escalated rats though there is greater attenuation of cocaine intake in stress-escalated rats. Studies examining CB1R density in the NAc shell and VTA following SA under stress and non-stress conditions are ongoing. These data suggest that repeated stress recruits eCB signaling in the NAc shell and VTA to drive drug use. Separate groups of rats were tested for reinstatement of drug-seeking behavior to a priming injection of cocaine (2.5, 5, or 10 mg/kg). Rats who received shock during SA demonstrated augmented reinstatement to all doses of cocaine. Furthermore, as with SA, the CB1R antagonist AM251 given prior to injection of cocaine (10 mg/kg, ip) significantly attenuated cocaine-primed reinstatement only in stress-escalated rats. These data suggest that stress-induced neuroplastic changes occur, likely in the eCB system, in regions of the brain that influence expression of escalated cocaine intake and augmented cocaine-primed reinstatement and these changes may be glucocorticoid-dependent. - Acknowledgements: Funded by NIH Grant DA15758 to John Mantsch (JM), NIDA Grant DA038663 to JM and CH, and NIDA Grant K01DA045295 to Jayme McReynolds

**Meyer HC, Lee FS**, Weill Cornell Medicine. *Developmental contributions of prefrontal and hippocampal circuitry to conditioned safety*
Anxiety disorders are highly prevalent, with diagnoses peaking during adolescence. Moreover, existing behavioral treatments to attenuate inappropriate fear responding in anxiety disorders have limited or no success for nearly half of the adolescent population. A critical barrier to developing treatments better suited for this group is a lack of knowledge about how key neural circuits related to fear acquisition and inhibition mature. Our lab has optimized a novel 'conditioned safety' paradigm appropriate for use in adolescent mice to address key basic science questions about safety learning with broad reaching translational and clinical value. Through this paradigm, mice learn to utilize stimuli explicitly predicting the absence of an aversive outcome (i.e., 'safety signals') in service of attenuating fear responding. Using this paradigm, marked age differences are apparent in the nature and strength of 'fear' and 'safety' properties inherent to respective stimuli. In addition, we have used fiber photometry in developing mice to link neural activity to real-time dynamics of safety and fear behavior via genetically encoded calcium indicators. Our findings indicate differential response patterns to conditions of fear and safety within subpopulations of hippocampal and prefrontal neurons, regions involved in the allocation and regulation of affective behaviors, and that undergo robust changes across adolescence.

**Miller, RR, & Polack, CW**, State University of New York at Binghamton. *TOTAL PREDICTIVE Error-Reduction Drives ACQUISITION of Associative Memories: No, No, and No*

A series of phenomena will be reviewed that indicate: a) Total Error Reduction modulates subsequent retrieval of associative memories, not acquisition; b) Local Error Reduction suffices to account for negatively accelerated acquisition curves; and c) the 'errors' that modulate acquisition and retrieval need not be predictive (i.e., forward). Collectively, these phenomena support discarding the dogma that 'Total Predictive Error-Reduction Drives Acquisition of Associative Memories,' and replacing it [less dogmatically] with 'Local discrepancy drives formation of associative memories, and total discrepancy modulates subsequent retrieval of associative memories.' - NIMH 033881

**Mohammadmirzaei N, Della Valle R, Knox D**, University of Delaware . *Effects of traumatic stress on fear and extinction memory in the conditioned suppression paradigm.*
Trauma exposure can lead to psychiatric disorders such as post-traumatic stress disorder (PTSD). Single prolonged stress (SPS) is a frequently used animal model of PTSD that mimics behavioral and psychological characteristics of PTSD such as persistent fear and anxiety. A commonly used behavioral paradigm for studying the effect of PTSD on fear memory and extinction learning is combining stress protocols with Pavlovian fear conditioning. The effect of SPS on fear memory and extinction learning is then determined by comparing different fear behaviors between SPS exposed animals and control groups. Interestingly, a careful review of the literature suggests that the circuits that facilitate emotional memory vary when different behavioral paradigms are used to measure emotional memory. In this study, we examined the effect of SPS on fear and extinction memory in the conditioned suppression paradigm. Animals were first trained on a FR3-30 criterion schedule (press bar 3 times under 30 seconds to get reward) before commencing SPS. After SPS, animals were re-examined on FR3-30 performance, then subjected to fear conditioning, extinction training, and extinction testing. First, the operant performances of animals before and after SPS exposure were compared. Preliminary data shows that 7 days after SPS exposure both control and SPS groups have faster operant performance. However, the increase in performance in SPS exposed animals was less than the control group indicating that SPS may decrease the elevated operant performance caused by 7-day interval with no rewards. The effect of SPS on different fear behaviors during fear conditioning, extinction training and testing was measured. Three fear behaviors were measured in this experiment; 1) freezing, 2) conditioned suppression, and 3) avoidance of the spatial location of the CS. Preliminary findings suggests that SPS animals show more conditioned suppression in comparison to the control groups and they acquire the conditioned suppression extinction memory more rapidly during the extinction training session. Moreover, there was an increase in freezing induced by CS during extinction training and testing in SPS animals. Surprisingly, control animals approached the location of the CS with CS presentation and this response was attenuated in SPS rats. The study is ongoing, but the findings suggest that behavioral paradigms that employ multiple measures of fear may provide more insight into how traumatic stress impacts emotional memory.

**Muller Ewald VA, LaLumiere RT**, Department of Psychological and Brain Sciences, Interdisciplinary Neuroscience Program, University of Iowa, Iowa City, IA. *When to seek and when to stop: changes in rodent infralimbic cortical neuronal activity during extinction learning following cocaine self-administration*
Prior work has implicated the rodent infralimbic cortex (IL) in the consolidation of extinction learning following cocaine self-administration. However, most studies investigating this cortical region employ manipulations of the IL, and little work has observed endogenous IL neuronal activity during the extinction of cocaine seeking. To determine how IL activity relates to extinction learning, we used in vivo electrophysiology to record from the IL of behaving rats as they underwent extinction training following cocaine self-administration. Male Sprague-Dawley rats (250 - 275 g) underwent surgery for implantation of an intravenous catheter and a fixed electrode array aimed unilaterally ate the IL, followed by cocaine self-administration for a minimum of 15 consecutive days. During self-administration, a light signaled the beginning of a 30 s availability period, during which a lever press was rewarded with a cocaine infusion, followed by immediate retraction of the lever and an intertrial interval. If animals failed to respond within the availability period, the lever was retracted and intertrial interval ensued. Following self-administration, animals underwent extinction training for a minimum of 8 days, during which recordings were conducted every day, and data were analyzed for the early, middle and late extinction time points. Extinction training involved the same behavioral paradigm as self-administration, however, lever presses did not produce cocaine infusions. Findings indicate that subpopulations of IL units differentially modulate their firing to non-rewarded lever presses and/or to the onset of the availability signal. IL units also show changes in firing dynamics, such as increases in baseline firing rates and burst firing during the progression of extinction training, as animals learn to withhold lever pressing. Together with prior work using brain-based manipulations, these findings suggest that changes in IL activity may guide behavioral outcomes during the extinction of cocaine-seeking behavior.

**Nett KE, Alizo V, LaLumiere RT**, Interdisciplinary Graduate Program in Neuroscience, Department of Psychological and Brain Sciences. *Model of craving for high-fat/high-sugar food in rats*
Considerable work has investigated the neurobiological mechanisms underlying drug addiction and the consumption of highly palatable food, especially those foods that increase the risk of obesity. Although clinical evidence suggests that "craving" is a significant symptom in each problem, little work has attempted to investigate how the neurobiological mechanisms involved in craving for highly palatable food compares and contrasts to those involved in drug seeking. Indeed, whereas much evidence suggests that a variety of prefrontal cortical systems regulate drug-seeking behavior, little research has examined such systems in the "craving" for highly palatable food. This dearth of research likely results from the relatively little research that has combined the well-established behavioral paradigms for investigating drug craving in rodents with the use of highly palatable foods that are known to increase body weight. Therefore, to address this issue, we created a behavioral paradigm that mirrors those used in drug craving except that the rats engage in a motivated behavior (lever pressing) to receive a high-fat/high-sugar (HFHS) food pellet (23.4% fat and 44.2% sugar). This behavioral paradigm uses a "long-access" self-administration period (6 h/d) to mimic studies with drugs of abuse, allowing the

rats to engage in instrumental behavior for a large consumption of HFHS food. In our pilot work, male Sprague-Dawley rats initially underwent self-administration for 1 h/d. They began on a fixed-ratio 1 (FR1) schedule for 6 d before switching to FR3 and eventually FR5 schedules of self-administration. The reinforcer was the delivery of a HFHS food pellet coupled with a light and tone cue. After reaching stable pellet consumption on the FR5 schedule, rats then underwent 7 d of FR5 reinforcement for 6 h/d. Following completion of all schedules of HFHS self-administration, rats underwent at least 7 d of 1 hr extinction training, in which an active lever press had no consequence. After successful extinction, rats then underwent both food-primed and cue-induced reinstatements in a counter-balanced manner. There was also a comparison group that underwent similar procedures but received standard rat chow pellets instead. All rats were given food ad libitum in their home cages. Rats readily self-administered both HFHS and regular chow pellets at each schedule of self-administration. Additionally, the rats were then able to extinguish to a baseline and reinstated seeking behavior for both food-primed and cue-induced methods of reinstatement. No significant differences appeared between the HFHS and chow groups, with the exception of the rate of extinction, where HFHS-administering rats extinguished their lever pressing faster. Overall, this work establishes the use of this paradigm as an approach for comparing the craving of highly rewarding food with that of craving for drugs of abuse. With this protocol, we can now engage in direct manipulations of prefrontal regions to determine their role in HFHS food seeking.

**Ng KH, Sangha S**, Purdue University , Department of Psychological Sciences, Purdue Institute for Integrative Neuroscience. *Changes in infralimbic cortical activity during conditioned inhibition of fear*

Expressing fear behavior in the absence of a threat is maladaptive because it decreases an organism's opportunity to seek life-sustaining substances. Learned safety signals can rescue the organism from this immobilizing state to resume exploratory behaviors. The infralimbic (IL) region of the prefrontal cortex is critical for fear extinction consolidation (Hikind & Maroun, 2008; Milad & Quirk, 2002) and to suppress fear in the presence of a safety cue (Sangha et al., 2014). IL neurons also show increased activity to an extinguished fear cue during the recall of fear extinction memory (Milad & Quirk, 2002). We thus hypothesized that IL neurons also encode for safety signals that are actively suppressing fear behavior in a situation that may be perceived as potentially dangerous. We recorded from IL neurons using multi-array electrodes during a fear-reward-safety cue discrimination paradigm that is well established in our laboratory (Sangha et al., 2013; Sangha, Greba, et al., 2014; Sangha, Robinson, et al., 2014; Ng et al., 2018). In this task, rats learn that the fear cue will result in a footshock, but when simultaneously presented with the safety cue as a compound cue (fear+safety cue), there is no footshock; male rats subsequently show high freezing to the fear cue and significantly lower freezing to the fear+safety cue. Our preliminary multi-unit data show that IL neurons increase their firing to the combined fear+safety cue when compared to the safety cue or fear cue alone, as well as increased firing to the reward cue. IL neurons also showed increased firing during reward consumption behavior. At the single unit level, both excitations and inhibitions were detected to individual cues. These data suggest that conditioned inhibition of fear via a safety cue and conditioned reward seeking in response to a reward cue may both engage an overlapping neural circuit within the IL. - This work was supported by the National Institute of Mental Health under award number R01MH110425

**Orsi SA, Devulapalli RK, Surineni R, Jarome TJ**, Animal and Poultry Sciences and School of Neuroscience, Virginia Polytechnic Institute and State University. *Distinct subcellular changes in proteasome activity and linkage-specific protein polyubiquitination in the amygdala during the consolidation and reconsolidation of a fear memory*

Numerous studies have supported a critical role for the ubiquitin-proteasome system (UPS) in the memory consolidation and reconsolidation processes. The protein targets and functional role of ubiquitin-proteasome activity can vary widely across cellular compartments, however, it is unknown how UPS activity changes within the nuclear, cytoplasmic, and synaptic regions in response to learning or memory retrieval. Additionally, while previous studies have focused on degradation-specific protein polyubiquitination, it is unknown how learning alters other polyubiquitin tags that are not targeted by the proteasome. Using cellular fractionation protocols in combination with linkage-specific polyubiquitin antibodies, we examined subcellular changes in ubiquitin-proteasome activity in the amygdala during memory consolidation and reconsolidation. Following memory acquisition, overall protein ubiquitination and proteasome activity simultaneously increased in the nucleus and decreased in the synaptic and cytoplasmic regions. The nuclear increases were associated with upregulation of degradation-specific (K48) and degradation-independent (K63, M1) polyubiquitin tags, suggesting multiple functions for ubiquitin signaling within this region. Interestingly, retrieval induced a very different pattern of ubiquitin-proteasome activity in the amygdala, consisting of increases in overall protein ubiquitination and proteasome activity and K48-, K63-, and M1-polyubiquitin tags in the synaptic, but not nuclear or cytoplasmic regions. Collectively, learning and memory retrieval dynamically and differentially alter degradation-dependent and degradation-independent ubiquitin-proteasome activity across different cellular compartments, suggesting that the UPS may serve unique functions during memory consolidation and reconsolidation.

**Pajser A, Foster C, Weston A, Pickens CL**, Kansas State University . *Naltrexone administration during extended fear conditioning prevents low pre-incubated fear in the fear incubation model*

Previous research has shown that extended fear conditioning leads to initially low fear that grows over time, often termed fear incubation. This is contrary to the pattern seen after limited fear conditioning, which results in high fear initially that is sustained over time. The neurobiological basis of these differences is unknown. One possibility is that endogenous opiates are released over the course of extended training, decreasing sensitivity to the fear-inducing stimulus. This could lead to the conditioned cues being associated with an ineffective shock, causing decreased fear. The current study was designed to investigate this possibility by blocking endogenous opiate activity during fear training via naltrexone administration. Male Long-Evans rats (n=8-12/group) acquired lever-pressing and then underwent training. During these training sessions, the rats experi-

enced 10 30-sec tones pseudo-randomly throughout the 90-min session, with some groups experiencing the tones co-terminating with a 0.5-sec foot-shock. There were 5 groups of experimental subjects. One group received 1 day of training with tone-shock pairings. Four other groups received 10 days of training with tone presentation, with 2 groups receiving tones alone and 2 groups receiving tones paired with shocks. Crossed with tone or tone-shock designation, two groups received injections of naltrexone (7 mg/kg, s.c.) before training days 2-10, and two groups received saline injections on these days. The day after fear conditioning was completed, animals underwent a contextual fear test, and the following day they underwent a cued fear test. After one month of incubation, animals underwent a contextual fear test again, and a cued fear test the following day. No injections were given before the tests. Fear was measured using with conditioned suppression of lever-pressing. We found that the group given 10 tone-shock sessions + 9 saline injections showed the pattern of behavior typically seen across the course of training in the extended training fear incubation paradigm: fear that decreases across training with low fear in the day 2 test that increased when tested one month later. However, the corresponding naltrexone group did not show the same decrease in fear across training, and fear was high in the day 2 test and remained steady at the 1 month test, similar to the pattern seen in group given 1 day of training. This suggests that the neurobiological basis behind the extended training fear incubation paradigm may be the release of endogenous opioids that develops throughout the course of training. - This project was supported by a grant from the National Institute of General Medical Science GM113109 of the National Institutes of Health

**Panoz-Brown D, Crystal JD**, Indiana University. *Replay of Episodic Memories in the Rat*

Vivid episodic memories in people have been characterized as the replay of multiple unique events in sequential order. Although we recently showed that rats remember multiple unique events in context, it is currently unknown if animals "replay" a stream of episodic memories to remember the order in which they occurred. Therefore, we developed an animal model of episodic memory replay. Here, we show that rats can remember a trial-unique stream of events and the order in which they occurred by engaging hippocampal-dependent episodic memory replay (Panoz-Brown et al., 2018, Current Biology). We document that rats rely on episodic memory replay to remember the order of events rather than relying on non-episodic memories. Replay of episodic memories survives a long retention-interval challenge and interference from the memory of other events, which documents that replay is part of long-term episodic memory. Further, the hippocampus has been shown to play a critical role in episodic memories in both people and rodents. Thus, to demonstrate that episodic memory replay relies on the hippocampus, we temporarily suppressed hippocampal activity using a chemogenetic approach employing designer receptors exclusively activated by designer drugs (DREADD). The chemogenetic activating drug clozapine N-oxide(CNO), but not vehicle, reversibly impairs episodic memory replay in rats previously injected bilaterally in the hippocampus with an inhibitory DREADD. By contrast, two non-episodic memory assessments are unaffected by CNO, showing selectivity of this hippocampal-dependent impairment. Our approach provides an animal model of episodic memory replay, a process by which the rat searches its representations in episodic memory in sequential order to find information. - AG053524 and AG051753

**Parker K**, University of Iowa. *Cerebellar Circuits, Timing, and Cognition*

Although the canonical role of the cerebellum is in motor function, accumulating evidence advocates for an anatomically distinct region of the cerebellum being involved in cognitive processing. Work by our group and others indicates that cerebellar modulation of the frontal cortex may be a key component to the cerebellar role in cognition. Cerebellar-frontal connectivity is conserved from rodents to humans making this circuit ideal for translational research. Dysfunction of this circuit may underlie diseases such as schizophrenia, autism and bipolar disorder. Additionally, several independent research groups have implicated the cerebellum as a novel therapeutic target for cognitive dysfunction in schizophrenia. We seek to understand how the cerebellum can be targeted therapeutically to restore cognitive function and we study this problem in detail by investigating how the cerebellum computes and communicates temporal information. Behavioral tasks requiring temporal processing are well-suited to study cognition because they require attention to elapsed time which is a component of working memory. This computation depends on the cerebellar-frontal circuit, which is known to be impaired in schizophrenia, and is also engaged by animals and humans when presented with timing tasks. We present data indicating 2Hz optogenetic stimulation of cerebellar output pathways can reinstate frontal cortical oscillations and ramping activity of single neurons following frontal dopamine blockade, rescuing timing performance. We use a combination of optogenetics, pharmacology, and multi-site neuronal recordings in rodents to determine how the cerebellum computes and communicates temporal information. Insights from these data in rodents, combined with human EEG and transcranial cerebellar stimulation, have the potential to guide future therapies and inspire novel treatments for patients suffering from neuropsychiatric disease.

**Plakke B, McKinnell Z, Barton P, Starr M**, Kansas State Univ. Dept of Psychological Sci. *VPA (Valproic Acid) Model of Autism like behavior in Long-Evans Rats.*

According to the CDC approximately 1 in 68 children will be diagnosed with autism spectrum disorder, which is a developmental disorder effecting communication, social interactions, and repetitive behaviors. In order to develop better treatment strategies is important to understand the underlying neurobiology of the disorder. The VPA model is a well- known animal model of autism like behavior with both construct and face validity (Mabunga et al., 2015; Roullet et al., 2013). Women who were prescribed medications containing VPA to treat seizures and bi-polar disorder had increases in the number of children that developed ASD compared to the regular population (Chomiak et al., 2013; Dean et al., 2002). The VPA model mimics this by introducing VPA into the system of a pregnant dam and then the offspring are raised and tested. Our lab is using the VPA model to examine behavioral deficits between treated and untreated offspring. Pregnant dams were injected with VPA or saline and the offspring were reared to adulthood. Social behavior was analyzed with the three chamber social task and repetitive behavior

was analyzed a marble burying task. Preliminary results indicated VPA offspring spent less time with a novel rat compared to saline control animals, indicating a decrease in sociability. VPA offspring buried significantly more marbles compared to controls, indicating an increase in repetitive behavior. These results support previous findings and suggest that the VPA exposure was effective. Follow up experiments will begin to examine cognitive flexibility as well as possible neural differences between VPA treated and untreated offspring. - KSU- Plakke Start up Funds, NIGMS- GM113109 NIH

**Rabinak, CA**, Pharmacy Practice, Wayne State University. *Cannabinoid facilitation of fear extinction in patients with posttraumatic stress disorder: A potential therapeutic target*

Exaggerated fear responses are the hallmark of posttraumatic stress disorder (PTSD). Empirically-supported psychotherapy for PTSD, Prolonged Exposure (PE), involves repeated exposure to fear-linked cues to produce "extinction" of fear. PE is generally effective, but many patients exhibit incomplete extinction or fail to sustain extinction learning-related improvements over time. Recall of extinction learning depends on limbic-frontal brain networks (hippocampus [HPC], ventromedial prefrontal cortex [vmPFC]) and PTSD patients show decreased activity in these regions and poor extinction recall. Adjunct interventions that address vmPFC-HPC dysfunction and rescue extinction recall deficits could enhance the efficacy of PE for PTSD. Our prior work suggests that an acute oral dose of ÎŤ9-tetrahydrocannabinol (THC), prior to experimental fear extinction procedures in healthy volunteers, facilitates recall of extinction learning by increasing activation and functional connectivity of vmPFC-HPC. As extinction recall deficits and vmPFC-HPC dysfunction have been observed in PTSD, our preliminary findings indicate the cannabinoid system is a promising target to improve the efficacy and durability of learning during PE in treating PTSD (e.g., shortening treatment while strengthening and prolonging gains). However, direct tests of cannabinoid effects on recall of extinction learning and associated neural circuits have not yet been conducted with PTSD patients. This ongoing double-blind, placebo-controlled, randomized-group study uses a Pavlovian fear learning paradigm to examine the effect of THC (7.5mg) vs. placebo (PBO), administered prior to extinction learning, on brain activation (functional magnetic resonance imaging [fMRI]) and skin conductance (SCR) responses in 49 trauma-exposed adult volunteers with (n=24; PTSD) and without (n=34; trauma-exposed controls; TEC) PTSD and 20 non-exposed healthy controls (HCs), testing extinction recall 24 hours after extinction learning. Preliminary data suggest that acute THC (vs. PBO) administration prior to extinction learning in PTSD patients improves recall of extinction learning. In particular, PTSD patients who received PBO during fear extinction exhibited, as expected, poor extinction recall as evidenced by increased peripheral measures of fear (SCR and US expectancy ratings) to a conditioned stimulus (CS) that was previously extinguished (CS+E). In contrast, PTSD patients who received THC during fear extinction exhibited good extinction recall (significantly lower peripheral measures of fear, compared to PBO) and increased HPC activation to the CS+E during recall of extinction learning. There was no drug effect on extinction recall in either control group (TEC, HC). These findings provide the first evidence that pharmacological enhancement of recall of extinction learning is feasible in PTSD patients using cannabinoid system modulators. Ultimately, the cannabinoid system may serve as a promising target for innovative intervention strategies in PTSD and other fear learning-related disorders. - K01MH101123; R61MH111935; BBRF NARSAD Young Investigator Award

**Radulovic J, Yamawaki N, Jovasevic V, , Kevin CA, Meyer MA, Shepherd GMS**, Northwestern University, Chicago, IL 60611. *Memory Processing in Hippocampal-Retrosplenial Cortical Circuits*

Learning to associate stressful events with specific environmental contexts depends on excitatory transmission in the hippocampus, but how this information is transmitted to the neocortex for lasting memory storage is unclear. We identified dorsal hippocampal (DH) projections to the retrosplenial cortex (RSC), which arise mainly from the subiculum and contain either the vesicular glutamate transporter 1 (vGlut1) or vGlut2. Both vGlut1+ and vGlut2+ axons strongly excite and disynaptically inhibit RSC pyramidal neurons in superficial layers, but vGlut2+ axons trigger greater inhibition that spreads to deep layers, indicating that these pathways engage RSC circuits via partially redundant, partially differentiated cellular mechanisms. Using contextual fear conditioning in mice to model contextual associative memories, together with chemogenetic axonal silencing, we found that vGlut1+ projections are principally involved in processing recent context memories whereas vGlut2+ projections contribute to their long-lasting storage. On the other hand, reduced connectivity between DH and RSC restricted to the theta frequency, resulted in the formation of state-dependent memories. - NIMH MH108837, MH078064

**Rajbhandari AK, Octeau JC, Malvaez M, Chavez J, Nguyen L, Keces N, Waschek JA, Khakh BS, Fanselow MS**, University of California-Los Angeles. *Role of PACAP neuropeptide and PAC1 receptor system in the basomedial amygdala and intercalated cells in regulation of fear behaviors*

Fear responses are critical for survival. However, fear regulation via certain brain regions can go awry when individuals are exposed to extremely traumatic stimuli leading some individuals to develop anxiety-related disorders like post-traumatic stress disorder (PTSD). Various brain regions, particularly the amygdala, govern fear. The amygdala microcircuitry containing the intercalated cells (ICCs) that lie in the interface of basolateral amygdala complex (containing the lateral, basolateral and basomedial amygdala) and the central amygdala are important modulators of fear behavior. Several neuropeptide systems are part of the amygdala microcircuitry including the neuropeptide PACAP (pituitary adenylyl cyclase-activating peptide) and its G-protein coupled receptor PAC1. In this regard, it was reported that the PACAP and PAC1 receptors are linked to PTSD symptom severity at both genetic and epigenetic levels, and this link was stronger in females with PTSD. Interestingly, PACAP expression if very high in the basolateral complex and PAC1 receptors are highly expressed in the ICCs. Our results show that PACAPergic neurons are particularly highly expressed in the basomedial amygdala (BMA) which in turn innervate the ICCs. Optogenetic stimulation of BMA-PACAP neurons increases excitatory postsynaptic potential in ICC neurons and enhances cfos expression in this region as well, showing that BMA-PACAP neurons can modulate synaptic function of the ICCs. In

turn, AAV-Cre mediated deletion of PAC1 receptors from the ICCs of mice with floxed PAC1 receptors leads to alterations in contextual fear acquisition, generalization, retention or extinction behaviors in a sex-dependent manner. Male mice with PAC1 deletion in ICCs show increased fear generalization and decreased fear extinction, whereas female mice with PAC1 deletion from ICCs show decreased fear acquisition. These results indicate that PACAP/PAC1 system is poised to modulate fear in a dynamic manner via the amygdala microcircuitry containing the PAC1 receptors. This dynamic balance is significantly different in males and females. Further studies could reveal the mechanisms through which stimulation of BMA-PACAP system might alter fear behaviors differentially in male and female mice. - NRSA-F32 MH10721201A1 and NARSAD 26612 (AKR)

**Rankin, CH, Yu, AJ, Ardiel EL**, University of British Columbia. *Parallel and Differential Neuropeptide Signalling Pathways Mediate Short-Term Sensitization in Caenorhabditis elegans*
Short-term behavioural plasticity in non-associative learning allows an organism to quickly adjust its behavioural strategies and adapt to its immediate environment. We use a genetically tractable model organism, C. elegans, combined with well-established non-associative learning paradigms and a high-throughput behavioural tracking system to investigate the genetic and molecular underpinnings of short-term sensitization. In our studies, we discovered a novel form of sensitization, which occurs during habituation to increase locomotion. The PDF neuropeptides are required to coordinate habituation of one response component and sensitization of another component to promote escape as a result of repeated nociceptive stimulation. IN a second paradigm a nociceptive response is sensitized by mechanosensory stimulation. Sensitization of the nociceptive response is mediated by PDF-1, one of the two PDF neuropeptides, but not PDF-2. Our research demonstrates that PDF neuropeptides can differentially mediate different forms of short-term sensitization to behavioural strategies. - Funded by NSERC

**Ray MH, Russ AN, Eghosa EK, Lee E, McDannald MA**, Boston College. *Roles for the nucleus accumbens core, and its Gad1 subpopulation, in adaptive scaling of fear*
Environmental threats exist on a continuum from unlikely to certain. Adaptive behavior requires fear to scale to the level of threat. Such scaling would be maximally adaptive if observed rapidly following exposure to threat, and sustained thereafter. In two experiments, we examined roles for the nucleus accumbens core (NAcc), and its Gad1 subpopulation, in adaptive scaling of fear. In experiment 1, male Long Evans rats received bilateral neurotoxic NAcc lesions, deleting all neuron types, or sham surgery, leaving NAcc intact. In experiment 2, male and female Gad1-cre rats received bilateral NAcc viral infusions of pAAV-flex-taCasp3-TEVp (Casp3), selectively deleting NAcc Gad1 neuron types, or AAV-EF1a-DIO-EYFP (YFP), leaving Gad1 neurons intact. Following recovery, rats received 16 days of fear discrimination in which three auditory cues were associated with unique foot shock probabilities: danger (p = 1.00), uncertainty (p = 0.25), and safety (p = 0.00). Fear was measured with a cumulative suppression ratio starting with the first 100-ms of cue presentation and incrementing in 100-ms steps through the entire 10-s cue duration. In experiment 1, sham rats acquired excellent fear discrimination, showing high fear to danger, intermediate fear to uncertainty, and low fear to safety. NAcc lesioned rats failed to show the same degree of discrimination, exhibiting decreased fear to danger and increased fear to safety. This pattern was most evident when assessing fear in the first 2-s of cue onset. While shams showed evidence of discrimination in 600-ms, such discrimination was not observed in NAcc rats until nearly 2-s. The NAcc is then necessary for rapid and sustained adaptive scaling of fear. In experiment 2, YFP rats showed superior rapid fear discrimination compared to Casp3 rats. However, as cue presentation continued, discrimination emerged more rapidly in Casp3 rats than YFPs. Although pending full histology for the gad1 experiment, the results reveal the NAcc is essential to adaptive scaling of fear and its Gad1 subpopulation organizes the emergence of discrimination over cue presentation. - DA034010

**Santori A, Colucci P, Marinelli N, Morena M, Hill MN, Campolongo P**, Sapienza University of Rome; Hotchkiss Brain Institute, University of Calgary. *Endocannabinoid modulation of circadian- and stress-dependent effects on rat short-term memory*
Cannabinoid drugs often induce biphasic effects on cognitive and emotional behavior depending on the level of stress and emotional arousal at the time of drug consumption. The effects of stress on endocannabinoids appear to be regionally specific and time-dependent relative to exposure to stress. Stress-induced changes in corticosterone affect memory. We evaluated how different stress intensities after encoding influence rat short-term memory in an object recognition task, whether the effects depend on circadian variation of corticosterone and if exogenous augmentation of anandamide levels could restore any observed impairment. Mild forced swimming stress selectively impaired memory retention in rats tested in the morning, while the stronger forced swimming stress caused memory impairments, independently of the testing time. The anandamide hydrolysis inhibitor URB597 reverted these impairing effects of stress on memory performance, leaving memory unaltered in the non-impaired groups.

**Shilyansky C, Young NP, Ramakrishnan C, Quirin S, Deisseroth K**, Stanford, PAVA MIRECC. *Optical interrogation of memory related activity across the rodent default mode network*
Human neuroimaging literature prominently features the default mode network (DMN) as a clinically important brain-wide cognitive network. In both human and rodent, the DMN is defined by slow correlated low-frequency (<1Hz) resting-state BOLD dynamics. The DMN involves areas known to function together during memory consolidation and recall, including prefrontal cortical areas, retrosplenial cortex/posterior cingulate, hippocampus and thalamus. However, it remains unknown whether slow correlated DMN dynamics reflect neuronal activity and network connectivity supporting memory. Here, we directly examined memory related neuronal activity and connectivity simultaneously across multiple DMN areas by using multifiber photometry (MFP) in mice. We carried out optical measurement of calcium-dependent activity from distinct populations of excitatory neurons in four DMN areas (medial prefrontal cortex, retrosplenial cortex, ventral hippocampus, and medial dorsal thalamus) and a control non-DMN area (somatosensory cortex). Across these areas, neuronal dynamics were

examined in response to either 1). optogenetic stimulation at theta vs non-theta frequencies or 2). recent and remote recall of contextual conditioning. Effective connectivity of the DMN was measured using optogenetic stimulation of a single DMN area, the medial prefrontal cortex (mPFC). Stimulation at theta frequency (7Hz) resulted in greater excitatory responses in the three other DMN areas compared to the control non-DMN area. In contrast, stimulation of mPFC at 20Hz resulted in equivalent responses in DMN and control areas. This suggests effective connectivity within the DMN that favors memory-related patterns of activity. Next, neuronal dynamics in DMN were examined during recent (24 hour) and remote (16 day) recall of context conditioning. Interestingly, correlated activity specific to the DMN was found during both recent and remote recall. These data suggest an association of DMN dynamics with network-wide distributed memory processing, and set the stage for exploring the role of these dynamics in coordinating corticolimbic activity during remote recall in normal and pathological states. - Supported by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

**Shipman ML, Bouton ME, Green JT**, University of Vermont. *Chemogenetic inhibition of prelimbic cortex projections to dorsomedial striatum attenuates operant responding*
The prelimbic cortex (PL) has been well established as a mediator of minimally-trained operant behavior, both in the literature focused on its role in goal-directed behavior and in renewal. The dorsomedial striatum (DMS) has similarly been linked to goal-directed behavior. Recent evidence suggests that silencing PL projections to the DMS during acquisition attenuates goal-directed responding. Our previous work showed that pharmacological inactivation of the PL at time of test following six acquisition sessions also resulted in an attenuation of operant responding. We therefore utilized designer receptors exclusively activated by designer drugs (DREADDs) to test whether or not projections from the PL to the DMS mediate this effect. Rats underwent bilateral PL-targeted infusions of either a DREADD virus (AAV8-hSyn-hM4D(Gi)-mCherry) or a control virus (AAV8-hSyn-GFP). In addition, guide cannulae were implanted bilaterally in the DMS. Rats were tested with both CNO and vehicle infusions into the DMS. We found that rats that had received the DREADD virus, but not the control virus, showed attenuated responding when they received CNO microinfusions into the DMS, compared to vehicle infusions. A fluorescent microscope was used to confirm placement of infusions and cannulae as well as viral-mediated expression. These results support the growing literature that suggests that connections between the PL and DMS are important for the expression of minimally-trained operant responding. - University of Vermont College of Arts and Sciences and Department of Psychological Science

**Shumake J, Jones CE, Auchter A, Monfils MH**, University of Texas at Austin. *Heterogeneity of extinction phenotypes in rats*
Fear conditioning is widely employed to examine the mechanisms that underlie dysregulations of the fear system. Various manipulations are often used following fear acquisition to attenuate fear memories. In rodent studies, freezing is often the main output measure to quantify 'fear'. Here, we developed data-driven criteria for defining a standard benchmark that indicates remission from conditioned fear and for identifying subgroups with differential treatment responses. These analyses will enable a better understanding of individual differences in treatment responding.

**Smith NJ, Trott JM, and Fanselow MS**, UCLA and Staglin Center for Brain & Behavioral Health, Department of Psychology, UCLA, Los Angeles, CA90095. *Fear, Avoidance and Punishment: Contribution of Pavlovian vs. Instrumental Processes*
Recently, the study of avoidance learning has seen a resurgence. This is in part fueled by a semantic error that equates the word "avoidance" as it is used in psychiatry and by laymen as opposed to how the term is used by learning theorists. To the learning theorist avoidance implies a behavior that precludes an aversive event in the future and that that behavior is acquired and maintained by a reinforcement contingency such as the response contingent termination of a warning signal or elimination of an impending aversive outcome. The psychiatric and lay usage is agnostic about the necessity of such contingencies. However, recent studies imply that fear related behavior can be altered by such contingencies and that they even offer a form of "proactive coping (e.g., Boeke et al., 2017)". The hypothesis that a frightened animal's behavior can be altered by reinforcement contingencies is in stark contrast to biologically oriented views of fear that argue that fear limits behavioral repertoires to species-specific defense reactions (SSDRs) that cannot be controlled by instrumental contingencies. Therefore, we tested between these antithetical positions. Male and female rats (Long-Evans and Sprague-Dawleys) were placed in a situation where the dominant SSDR, freezing, during an auditory warning signal, could either avoid, or was punished by, an aversive footshock (.8mA; 1-sec). These schedules produced high levels of freezing (30-80%) that showed little difference between groups except for a trend for freezing to be more pronounced when it was punished than when it avoided shock. In other words, the available operant contingencies (CS termination and shock avoidance) provided no evidence for instrumental control of behavior. The most striking difference between groups was that rats in the punished condition received far more shocks than the avoidance animals. Similar findings were reported by Bolles & Riley (1972) who used a free-operant rather than the discrete trial design used here. The failure for punishment to suppress freezing is particularly damning to reinforcement theories as those animals could both avoid the shock and terminate the CS by doing anything other than freezing. That is, in our punishment arrangement any response that the animal cares to make other than freezing is effectively an active avoidance response. The behavior of not freezing occurred at a sufficient rate to contact the available reinforcement contingencies yet the animals could not acquire the other-than-freeze response. The observed fear-related behavior was fully predicted by the most basic of Pavlovian principles, CS-US association. Because fear produced by the tone elicited freezing, punishment animals received a higher probability of CS-US pairing than avoidance animals. These findings have major implications for the use and interpretation of avoidance learning as a method for studying fear. As argued over 40 years ago (Bolles, 1975, p 364), "no response learning occurs in the avoidance situation." - NIH RO1 MH062122

**Stephen C. Gironda, Benjamin J. De Corte, & Matthew S.**

**Matell** , Villanova Univerisity Department of Psychological and Brain Sciences, Iowa Neuroscience Institute. *Relational Encoding of Time across Modalities in the Peak Procedure*

Previous work from our lab (De Corte et al., in revision) showed that rats recalibrate their temporal expectations of one cue-signaled duration, after being re-trained with a different cue-signaled duration. Specifically, subjects were trained on a peak-interval procedure that cue 1 (e.g., tone) signified a 8s fixed-interval, while cue 2 (e.g., light) indicated a 16s fixed-interval. In a subsequent re-training phase, cue 2's fixed interval was extended to 32s, and exposure to cue 1 was halted. After temporal control to cue 2 was established at the new peak time, testing of cue 1 revealed that subjects shifted their expectation for that cue in the same direction (i.e., a 59% rightward shift). To assess how this effect would generalize to other duration ratios, in experiment 1,âĂŕwe used a 4s interval for cue 1 and a 16sâĂŕintervalâĂŕfor cue 2. Following re-training of cue 2âĂŕto 32s, testing of cue 1 demonstrated no significant shift (median shift = 2.2%). In Experiment 2, we trained separate groups of rats on different interval ratios with cue 1 (tone) at 8 s, 12 s, or 24 s and cue 2 (light) at 16 s. Following re-training of cue 2 to 32s, we found that cue 1's rightward shift (as a percentage of initial peak time) grew in direct proportion to the initial temporal ratio between the two cues (r2= .62, p<0.001). However, cue 1 shifts were significantly smaller than the 100% increase in cue 2 (p<.001), suggesting that subjects tempered their recalibrated expectation by the initial, absolute duration of cue 1.âĂŕ Indeed, a model utilizing a weighted average of an absolute expectation and a ratio-maintained shifted expectation accounted for 83% of the variance in the data. This evidence suggests that rats encode both the absolute and relative relationship between temporal cues from different modalities.âĂŕ-DA039405

**Stern SA, Azevedo EP, Doerig K, Pomeranz LE, Friedman JM**, The Rockefeller University. *A molecularly defined insular→central amygdala circuit controls cue-mediated overconsumption*

The ability to molecularly define cell types controlling complex behaviors would greatly enhance our ability to study these behaviors and underlying circuitry. Feeding is a complex motivated behavior that is controlled not just by metabolic and homeostatic factors, but also by environmental factors such as emotion and the hedonic nature of the food itself. Yet, little is known about how brain regions involved in cognition and emotion might contribute to overeating, and therefore, obesity. Recently, we developed and validated a simple and rapid context-induced feeding (Ctx-IF) task in which cues associated with food availability can later lead to increased food consumption in sated mice (Stern et al. Molecular Psychiatry 2018). We have used this paradigm to map brain regions that are activated during Ctx-IF and found that the insular cortex (IC) and central amygdala (CeA), among others, are activated in sated mice following exposure to cues denoting the availability of food. The IC is a region critical for taste perception that has recently been shown to be involved in cue-food associations and taste memory. Here, we find that the insular cortex, and specifically, the IC→CeA projection, is required for overconsumption in the Ctx-IF task. To probe the molecular connectivity of these two regions, we used the recently developed method, retro-TRAP (Retrograde - Translating Ribosome Affinity Purification), to profile projections from the IC to the CeA. We injected the retrograde canine adenovirus, CAV-GFP, into the CeA of SYN-NBL10 mice which contain anti-GFP–tagged ribosomal subunit proteins. Two weeks later, we dissected out the insular cortex and immunoprecipitated GFP, therefore pulling down polysome-bound, translating mRNAs of neurons that project to CeA. High throughput RNA-sequencing has enabled us to identify markers for projections from IC to CeA, including neuronal nitric oxide synthase 1 (Nos1) and vesicular glutamate transporter 2 (Vglut2), and therefore to investigate the role of these projections in the non-homeostatic regulation of feeding behavior. - NRSA F32DK107077; JPB Foundation

**Tavakkoli A, Bucci DJ, & Todd TP**, Department of Psychological and Brain Sciences Dartmouth College, Hanover, NH. *Pre-training lesions of dorsal hippocampus do not weaken ABC renewal of conditioned suppression*

Extinction of fear to a conditioned stimulus (CS) is a context-dependent; removal from the extinction context results in renewal of conditioned fear to the CS (Bouton & Bolles, 1979). Prior experiments have demonstrated a critical role for the dorsal hippocampus (DH) in fear renewal. However, the majority these studies examined renewal in conditioned freezing procedures. The role of the DH in renewal is less clear in other procedures, such as conditioned suppression. For example, pre-training fornix lesions or pre-training neurotoxic lesions of the DH have no impact on renewal of conditioned suppression (Frohardt et al., 2000; Wilson et al., 1995). Likewise, post-extinction lesions of the DH do not weaken renewal of conditioned suppression (Todd et al., 2017). Since all prior conditioned suppression experiments examined ABA renewal, which involves a return to the original conditioning context, the current study examined the impact of pre-training DH lesions on ABC renewal. ABC renewal isolates the contextual retrieval of extinction, because it does not involve a return to the original conditioning context. Both Sham and DH lesioned rats received light-shock pairings in Context A, followed by extinction in Context B. Although fear was reduced to the CS in Context B, it renewed when presented in an equally familiar Context C. Further, the renewal effect did not interact with group; both Sham and DH lesioned rats demonstrated ABC renewal. Summation testing revealed that the extinction context was not a conditioned inhibitor, and likely controlled extinction responding by modulating the light-shock association. DH lesions did disrupt other aspects of behavior, such as the acquisition of lever-pressing, and initial unconditioned suppression during pre-exposure to both the light and click cues. Overall, this experiment suggests that the DH is not necessary for renewal resulting from removal from the extinction context. Future studies will examine the impact of post-training lesions, and / or temporary inactivation at the time of test.

**Trask S, Ferrara NC, Helmstetter FJ**, University of Wisconsin - Milwaukee. *Optogenetic silencing of the thalamo-amygdala pathway, but not lateral amygdala, results in a long-term decrease in fear expression*

Pavlovian fear conditioning, in which a previously neutral conditional stimulus (CS) is paired with an aversive unconditional stimulus (US), represents one process by which aversive memories are formed. Retrieval trials, in which the CS is presented without the

US, results in an increased lability of the memory and thus presents a good opportunity for memory modification. Previous work from this laboratory has demonstrated that transient optogenetic silencing of the projection from the auditory thalamus to the amygdala during fear recall results in a context-specific decrease in responding during a laser-free test. The current experiments aimed to expand upon this finding. In an initial experiment, rats were given presentations of an auditory CS coterminating with a 1 mA footshock. The following day, animals were given 4 retrieval trials in a shifted context, during which input from the auditory thalamus (i.e., MgN) to the amygdala was silenced using the light-driven proton pump ArchT (AAV9-CAG-ArchT-GFP). Rats were tested for memory retention as indicated by freezing to the CS either one or 14 days following retrieval in test session without neural silencing. Both groups showed a reduction in responding during retrieval that persisted to the light-free test. Thus, silencing the thalamo-amygdala pathway during retrieval results in a long-term decrease in fear memory. However,it remains unclear whether or not this persistent decrease is specifically related to the MgN-BLA connection. In a second experiment using the same training procedures and testing procedures, rats received optogenetic inactivation of local neurons in the lateral amygdala (rather than the MgN-BLA terminals) during retrieval. Despite replicating the inhibition-driven decrease in freezing to the CS during retrieval, this effect did not persist to the inhibition-free test the next day. Together, these results demonstrate that while inactivating the amygdala does impair performance at memory retrieval, only silencing the thalamo-amygdala pathway results in a persistent decrease in fear expression. - NIMH R01 MH069558 to FJH

**Urien L, Cohen S, Jinich S, Nordlicht R, Bauer EP**, Barnard College. *Contextual fear conditioning differentially activates extended amygdala circuits in male and female rats*

The Bed Nucleus of the Stria Terminalis (BNST) has long been described for its contribution to anxiety, stress responses and contextual fear conditioning. However, most of these studies have been performed in male rodents whereas it is known that the BNST is a sexually dimorphic structure. We thus decided to test the contribution of the BNST to contextual fear in females. Animals received three unsignaled shocks and were tested for expression of context fear for 10 minutes 24 hours later. Non-specific extensive lesions of the BNST with ibotenic acid blocked expression of contextual fear expression in both sexes. Interestingly, context fear expression was associated with upregulation of the immediate-early genes ARC and FOS in the anterolateral portion of the BNST (BNST_AL) in male rats but not in females. Indeed we rather see increased neuronal activity in the central nucleus of the amygdala in females. Accordingly, we have started investigation of targeted BNST_AL-amygdala pathways in males and females that could unravel very specific sexually dimorphic mechanisms of contextual fear expression.

**Vega Villar, M, Horvitz, JC, Nicola, SM**, The Graduate Center, CUNY, New York, NY; Dept. of Neuroscience, Albert Einstein College of Medicine, Bronx, NY.. *Acquisition of a cued approach response requires NMDA receptor-dependent potentiation of cue-evoked excitations in the nucleus accumbens core.*

Appetitive conditioning, a form of associative learning that allows animals to seek rewards relying on environmental cues that act as predictors, is a fundamental aspect of adaptive behavior. Many nucleus accumbens (NAc) neurons are excited or inhibited upon presentation of an already-learned reward-predictive cue. These signals encode the motivational value of the cue and are required for expression of approach behavior prompted by the cue (McGinty et al., Neuron 2013; Du Hoffmann and Nicola, J Neurosci 2014). However, whether and how these signals emerge throughout training has not been established. In Experiment 1, we recorded the unit firing activity of NAc core neurons as rats learned a cued approach task. Our results indicate that cue-evoked excitations appear in many neurons a few trials before rats begin to respond consistently to the cue. Because infusion of NMDA receptor antagonists into the NAc during training impairs acquisition of similar reward-oriented behaviors (e.g. Di Ciano et al., J Neurosci 2001), we hypothesized that the emergence of cue-evoked excitations during cued approach learning is due to NMDA receptor-dependent plasticity within the NAc. In Experiment 2, we performed colocalized simultaneous unit recordings and NMDA antagonist microinfusions in the NAc. We found that injection of the NMDA antagonist AP5 into the NAc both impaired the emergence of cue-evoked excitations in NAc neurons and, when performed bilaterally, prevented learning. Strikingly, unilateral infusion of AP5 had the same effect on emergence of cue-evoked excitations in the AP5-injected NAc (but not the contralateral saline-injected NAc) while learning remained intact in most animals. Therefore, the drug's effects on firing cannot be explained by impaired behavioral performance. Finally, in a drug-free extinction test after training, cue-evoked excitations were smaller in the previously AP5-treated NAc than in the contralateral (previously saline-injected) NAc, indicating that AP5 prevents the induction of a lasting form of plasticity. These results demonstrate that NMDA receptor-dependent plasticity in the NAc potentiates the cue-evoked firing of NAc neurons, and that this form of plasticity is a key element of the mechanism by which cued appetitive approach is learned.

**Wahlstrom KL, LaLumiere RT**, University of Iowa. *Basolateral amygdala inputs to the medial entorhinal cortex in the consolidation of spatial and cued-response memory*

Previous work on multiple memory systems suggests that spatial learning is mediated by hippocampus-based systems and that the basolateral amygdala (BLA) modulates the consolidation for this type of learning. The medial entorhinal cortex (mEC) is a critical region in the hippocampus-based system for processing spatial information and, as an efferent target of the BLA, is the likely mechanism by which the BLA influences spatial learning. Therefore, the present study examined whether optically stimulating activity in the BLA-mEC pathway alters the consolidation of spatial learning. Previous studies also suggest that hippocampus-based and caudate-based systems compete in the consolidation of spatial and cued-response memory, respectively. Therefore, this study also examined whether optically stimulating the BLA-mEC pathway alters the consolidation of cued-response learning. To address these questions, the BLA of male Sprague-Dawley rats were transduced to express ChR2(E123A), and fiber optic probes were implanted in the mEC to provide illumination of BLA axons. A Barnes maze was used to assess learning. During the training trials, the escape

port of the maze was either located in the same position for each trial (spatial) or was marked with a distinct cue immediately above it, and the port and cue were moved in unison to a different cardinal direction for each trial (cued-response). Rats were given consecutive training trials on either task, followed immediately by 15 min of optical stimulation (8 or 40 Hz) of the BLA-mEC pathway. Rats were returned to the Barnes maze 2 d later for a single retention test. Rats that received 8 Hz but not 40 Hz optical stimulation of the BLA-mEC pathway following spatial and cued-response training had enhanced and impaired retention, respectively. These findings are consistent with the hypothesis that the neural systems mediating these two types of learning compete with one another. A follow-up study was conducted to examine ARC (activity-regulated cytoskeleton-associated protein), a plasticity-associated protein implicated in hippocampal-dependent learning and memory. Male and female Sprague-Dawley rats were trained on the spatial or cued-response version of the Barnes maze, and were sacrificed 1 h after the start of training. Brains were removed and flash-frozen and tissue punches were collected for ARC protein analysis. Western blot was used to determine the density of ARC protein in the dorsal hippocampus. Results revealed that there were significantly higher levels of ARC in the dorsal hippocampus of male and female rats that were trained on the spatial task compared to both the cued task and a no-training control group. - This research was supported by MH104384 (RTL).

**Wasserman, Edward, A.**, University of Iowa. *Precrastination, anticipation, and signalization: Implications for adaptive action*
Procrastination is a familiar and widely discussed proclivity: postponing tasks that can be done earlier. Precrastination is a lesser known and explored tendency: completing tasks quickly just to get them done sooner. Recent research suggests that precrastination may represent an important penchant that can be observed in both people and animals. I review evidence concerned with precrastination and connect that evidence with a long history of interest in anticipatory learning, distance reception, and brain evolution. I go on to encompass several related topics including impulsivity, planning, and self-control. Precrastination may be a new term in the psychological lexicon, but it may be a predisposition with an extended evolutionary history. Placing precrastination within the general rubric of anticipatory action may yield important insights into both adaptive and maladaptive behavior.

**Wassum KW, Malvaez, M, Lichtenberg N, Morse A, Shieh C, Murphy M, Greenfield V, Sepe-Forest L, Holley S, Cepeda C, Levine M**, UCLA. *Cortical-amygdala circuitry in reward encoding and retrieval*
To make adaptive decisions we must cast ourselves into the future and consider the outcomes of our potential choices. This prospective consideration is informed by our memories. I will discuss our lab's recent work investigating the neural circuits responsible for encoding, updating, and retrieving reward memories for use in the considerations underlying decision making. We have taken a multifaceted approach to these investigations, combining recording, modern circuit dissection, and behavioral tools. Our results are generally indicating that the orbitofrontal cortex and basolateral amygdala work in a circuit to participate in these functions. The cognitive symptoms underlying many psychiatric disorders result from a failure to appropriately learn about and/or anticipate potential future events, making these basic science data relevant to the understanding and potential treatment of mental illness. - DA035443

**Weiss C, Disterhoft JF**, Northwestern University Feinberg School of Medicine. *Basic and Translational Analyses of Eyeblink Conditioning in Rabbits and Mice*
Classical conditioning of the eyeblink reflex has been used for decades as a tractable behavioral paradigm to understand the neurobiological mechanisms of sensorimotor integration. These studies began with human subjects and then focused on the rabbit due to its large eyes, low spontaneous blink rate, and tolerance for restraint. More recently we and others have been utilizing the mouse to take advantage of modern genetic technologies. However, we also continue to utilize the rabbit for MRI-based analyses of conditioning, and as a non-transgenic model of Alzheimer's Disease (AD) given that the rabbit amino acid sequence for amyloid (the main component of AD plaques) is nearly identical to that of humans, its amino acid sequence encoding the microtubule stabilizing tau protein (the main component of neurofibrillary tangles) is similar in key regions, and its lipid physiology (a key risk factor for AD) is similar to that of humans. Our experiments utilize whisker vibration as a conditioning stimulus and an airpuff to the eye as the unconditioned stimulus. Our mice are head-fixed and free to ambulate upon a cylindrical treadmill while our rabbits are also head-fixed with their body swaddled in a bag inside of an acrylic restrainer. We are using inhibitory DREADDs in the mouse to determine the relative roles of the SI and SII whisker-related cortex during acquisition and recall of remotely conditioned blinks, and we are using dietary manipulations in the rabbit to induce AD-like neuronal pathology. More specifically, we feed our rabbits a diet enriched with either 2% cholesterol, or a diet enriched with either high fat or high sugar. These dietary manipulations are similar to diets in humans that lead to two risk factors for developing AD, i.e. high cholesterol and Type II diabetes. Our results in the mouse confirm our results in the rabbit, i.e. that SI cortex is required for acquisition of conditioned blinks and SII cortex is required for expression of remotely acquired memory, and our results in the diet manipulated rabbit indicate that either high cholesterol or high sugar lead to a loss of both object and place recognition and a significant amount of immunoreactivity for beta amyloid oligomers in frontal cortex. Our results support the use of modern genetic techniques in the mouse to understand the neurobiological basis of sensorimotor integration, and the use of rabbit to understand the molecular basis of risk factors that lead to AD–like cognitive deficits and neuronal pathology in a non-transgenic model system. - NIH R56AG050492 and Woman's Board of Northwestern Memorial Hospital

**Wiltgen, BJ**, UC Davis. *Mind the gap: Neural circuits underlying trace fear conditioning*
In trace conditioning, a temporal gap is inserted after the CS and before the onset of the US. Pavlov theorized that a 'memory trace' of the CS had to be maintained in the absence of the stimulus in order for animals for to learn the association. In this talk, I will briefly review the history of trace conditioning, describe theories about what is learned in this procedure and discuss the underlying neural cir-

cuitry. I will then present new data from my lab using optogenetic manipulations to probe the cellular mechanisms by which animals encode and retrieve trace fear conditioning. - NIH R01NS088053

**Yagi S, Galea LAM**, Graduate Program in Neuroscience, Department of Psychology, Djavad Mowafaghian Centre for Brain Health, University of British Columbia. *Sex and strategy differences in immediate early gene activation and neurogenesis in the hippocampus after pattern separation*

Sex differences are reported in hippocampal plasticity and cognition. The hippocampus is an important brain region for associative, declarative and episodic memory. A meta-analysis shows that males perform better at some forms of hippocampus dependent cognition compared to females both in humans and rodents. The hippocampus is a highly plastic structure including the ability to produce new neurons in the dentate gyrus, which plays an important role in pattern separation. Intriguingly, there are prominent sex differences in the level of neurogenesis and the activation of new neurons in response to hippocampus-dependent cognitive tasks in rodents. However, these sex differences in spatial navigation and the enhancement of adult neurogenesis after spatial learning tasks are dependent on learning strategy use. Recently, we demonstrated that male rats that rely more on a hippocampus-dependent spatial strategy were better at separating similar patterns in the radial arm maze compared to female spatial strategy users, while there was no significant sex difference among male and female rats with more reliance on striatum-dependent idiothetic response strategy. Furthermore, spatial navigation and pattern separation training enhanced adult neurogenesis only in male spatial strategy users, but no such increase was observed in idiothetic response strategy users or in females. We emphasize the importance of studying sex differences in learning strategy during spatial navigation and the strategy use dependent enhancement on hippocampal neural plasticity. Understanding sex differences in the contribution of hippocampal plasticity to cognition is important as it can give us important clues on the underlying mechanisms of sex differences in prevalence and severity of cognitive impairment seen in the neurological diseases such as Alzheimer's disease and depression.

**Zeid D, Kutlu MG, Gould TJ**, Penn State University, Department of Biobehavioral Health. *Differential susceptibility to effects of acute versus chronic nicotine on fear extinction and spontaneous recovery in adolescent mice*

Adolescent mice are differentially susceptible to the effects of both acute and chronic nicotine exposure on contextual fear learning relative to adults. This may result in differential vulnerabilities to nicotine addiction and related disorders between adolescents and adults. Here, we extend this finding by testing effects of acute and chronic nicotine exposure on adolescent fear extinction and spontaneous recovery (SR), a model of PTSD. We first examined the effects of acute nicotine administration on extinction and SR of contextual fear memories in pre-adolescent (PND 23), late adolescent (PND 38), and adult (PND 53) C57BL/6J mice. Mice were trained in a background contextual fear conditioning paradigm and given an intraperitoneal injection of one of four doses of nicotine prior to subsequent extinction or SR sessions. Pre-adolescent and late adolescent mice were found to be less sensitive than adults to acute nicotine's effects on extinction and SR. In a separate experiment, we tested the effects of chronic nicotine exposure in pre-adolescence on adulthood extinction and SR of fear memory in a model in which contextual fear acquisition occurred prior to nicotine exposure. Pre-adolescent and adult male C57BL/6J mice underwent contextual fear conditioning and were then exposed to chronic nicotine via osmotic minipump. Eighteen days following the removal of nicotine, both groups of mice underwent fear extinction, followed by a SR session a week later. It was found that, while history of chronic nicotine did not affect later extinction of fear memory in either pre-adolescent or adult mice, adult SR of fear memory was impaired in mice exposed to nicotine as adults and enhanced in mice exposed to nicotine as pre-adolescents. Together, these findings suggest that long-term, but not short-term, nicotine exposure in adolescence may predict susceptibility to reoccurrence of traumatic memories. - This work was funded with grant support from the National Institute on Drug Abuse (T.J.G., DA017949).

Program prepared by W. J. Wilson