Pavlovian Society Annual Meeting, 2017 Hilton Penns Landing

October 5–8, 2017

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

Overview

Thur	6:00–10:00 PM	Opening Reception Columbus Ballroom Hors d'Oeuvres & Cash Bar
Fri	7:30–8:25	Breakfast
	8:25–Noon	Morning Sessions
	12:05–1:30	Lunch (Exec Committee Meeting)
	1:30–5:15	Afternoon Sessions
	5:30–7:30	Posters & Cash Bar
Sat	7:30–8:25	Breakfast
	8:25–12:05	Morning Sessions
	12:05–1:40	Lunch (WIL Luncheon)
	1:40–5:10	Afternoon Sessions
	5:30–7:30	Posters & Cash Bar
	7:30–9:00	Banquet

Program

Friday (October 6)

7:30–8:25 **Breakfast**
Columbus Ballroom Foyer

8:25–8:30 **Mark Stanton** (University of Delaware) Welcome

8:30–9:00 **Delamater A** (Brooklyn-CUNY) Past-President Lecture: Learning about reward identity and time: A multi-component approach

9:00–10:30 **Symposium: Violence Against Women and the Formation of Trauma Memories (Tracey Shors, Chair)**

* **Brown LA, Foa EB** (U. Pennsylvania) Prolonged Exposure Therapy in the Recovery from Posttraumatic Stress Disorder

* **D'Andrea W** (The New School) The Importance of Engagement: Understanding the Importance of Physiological Arousal in Reducing the Impact of Trauma

* **Shors TJ** (Rutgers) Sexual Violence, Stressful Memories, and Learning to Recover

10:30–10:45 **Coffee Break**

Columbus Ballroom Foyer

10:45–12:05 **Symposium: Plasticity of Social Behavior (Moriel Zelikowsky, Chair)**

* **Zelikowsky M** (Cal Tech) Neuropeptidergic control of stress-induced effects on fear and social behavior

* **Lin D** (New York U.) The neural mechanism of aggressive motivation

* **Kennedy A** (CalTech) Social behavior shapes hypothalamic neural ensemble representations of conspecific sex

* **Gunaydin LA** (UCSF) Afferent control of striatal circuitry in social and anxiety-like behaviors

12:05–1:25 **Lunch (on your own)**
Executive Committee Meeting (The Admiral's Quarters)

1:25–1:45 **Fink AJP, Schoonover CE, Axel R** (Columbia) A naturalistic assay for measuring behavioral responses to aversive stimuli at millisecond timescale

1:45–3:25 **Symposium: A Spotlight on Attention Debra Bangasser, Chair)**

* **Bangasser DA** (Temple) Stress regulation of sustained attention

* **Young JW, Light GL** (UCSD) Attentional assessment across species reveal putative mechanisms, biomarkers, and treatments for clinical populations

* **Saksida LM** (Western U., Canada) Assessing Attention in Rodent Models of Alzheimer's Disease and Schizophrenia

* **Kastner S** (Princeton) Neural network dynamics for attentional selection

3:25–3:40 **Coffee Break**
Columbus Ballroom Foyer

3:40–5:25 **Symposium: Associative Interference in Acquired Behavior (Ralph Miller, Chair)**

* **Miller RR, Polack CW** (Binghamton) Associative Interference as a Major Source of Forgetting in Pavlovian Conditioning and the Fate of Forgotten Associations

* **Rosas JM et al.** (U. Jaen, Spain) Associative Interference Facilitates Subsequent New Learning
* **Bouton ME** (U. Vermont) Contextual Control of Retroactive Inhibition in Instrumental Learning

5:30—7:30 **Posters and Cash Bar**
Columbus Ballroom Foyer

Saturday (Oct 7)

7:30–8:25 **Breakfast**
Columbus Ballroom Foyer
Sessions in Columbus Ballroom

8:25–8:30 **Mark Stanton** (U. Delaware) Welcome

8:30–9:50 **Invited Talks**
* **Beckers T** (KU Lueven, Belgium) Generalization and post-retrieval amnesia
* **Cheng DT** (Auburn) Alcohol Effects on Behavior and Brain Function during Human Eyeblink Conditioning
* **Sangha S** (Purdue) Neural circuits of inhibiting conditioned fear by a safety cue in a fear-safety-reward cue discrimination task
* **Callaghan B** (Columbia) Brain Bugs - Understanding the role of the gut microbiome in stress, learning, and mental health

9:50–10:20 **Phelps E** (NYU) Novel techniques to prevent the return of threat responses

10:20–10:35 **Coffee Break**
Columbus Ballroom Foyer

10:35–12:05 **Symposium: Social Communication (Josh Neunuebel, Chair)**
* **Neunuebel J** (U. Delaware) Social context-dependent ultrasonic vocal signaling in mice
* **Fortune E** (NJ Inst Tech) When Brains Co-operate
* **Zhao L** (Johns Hopkins) Adaptive Vocal Control by Marmosets in Social Communication

12:05–1:40 **Lunch / Women in Learning satellite meeting**
See last page of Program

1:40–2:20 **Invited Talks**
* **Fast CD, Ellis H, Webb EK, Lewon M, Brotheridge S, Cox C** (APOPO, Belgium) Investigating peak shift in an olfactory discrimination: Lessons for animal scent detection
* **Bath KG, Manzano-Nieves G, Bravo M, Johnsen A** (Brown) ELS is associated with precocious amygdala development and an unexpected dip in threat-associated freezing

2:20–3:20 **Gallagher M** (Johns Hopkins) Keynote Address: The Two-Way Street Linking Rodent and Primate Brains in Translational Research

3:20–3:40 **Coffee Break**
Columbus Ballroom Foyer

3:40–5:10	**Symposium: Neurobiology of Infantile Amnesia (Mark Stanton, Chair)** * **Madsen HB, Kim JH** (Florey Institute) Sex differences in the ontogeny of mem ory - A double dissociation between extinction and infantile amnesia * **Frankland PW** (U. Toronto) Optogenetic recovery of 'lost' infantile memories * **Travaglia A, Bisaz R, Steinmetz AB, Miranda JM, Sweet ES, Blitzer RD, Alberini CM** (New York U) Latent infantile memories and critical period mechanisms
5:30–7:30	**Posters and Cash Bar** Columbus Ballroom Hallway
7:30–9:00	**Banquet** Columbus Ballroom Speaker: **Chad Forbes** (University of Delaware) Social Threats as Catalysts for Learned Social Aversions Awards

1 Posters

Generally alphabetical by author except for some moved between days.

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

1. **Adkins JM, Gilman TL, Dutta S, Jasnow AM** Activation of Corticotropin-releasing factor (CRF) Neurons within the Central Nucleus of the Amygdala Reduces Fear Expression in Mice

2. **Akdogan B, Gallistel CR, Wanar A, Gersten BK, Balsam PD** Temporal Representations in the Duration Discrimination Task

3. **Alfei JM, Ferrer-Monti RI, Mugnaini M, Bueno AM, Beckers T, Urcelay GP, Molina VA** A comparison of behavioral and pharmacological interventions to attenuate reactivated fear memories

4. **Allen, MT, Blankenship, MR, Servatius, RJ** The Distressed (Type D) Personality Factor of Social Inhibition, but Not Negative Affectivity, Enhances Eyeblink Conditioning: Further Support for a Learning Diathesis Model of Anxiety Disorders

5. **Arnaudova I, Beckers T** Generalization of extinction: Examining fear recovery to conditioned and generalization stimuli following extinction with conditioned or generalization stimuli

6. **Bacharach SZ, Nasser HM, Dantrassy HM, Zlebnik NE, Cheer JF, Calu DJ** CB1 receptor signaling enhances stimulus value attribution in Pavlovian and instrumental settings

7. **Bailey C, Schnegelsiepen A, Stuebing S, Marshall AT, Peterson JR, Kirkpatrick K** Generalizability of Fixed-Interval Intervention on Impulsive Choice in Rats

8. **Beaver J, Dutta S, Gilman TL, Cecil C, Adkins JM, Jasnow AM** Thy1 Neuron Activation in BLA Promotes Fear Inhibition and Reduces Defeat-Induced Social Inhibition

9. **Ben-Ami Bartal I, Long K, Keltner D, Kaufer D** Neural substrates of pro-social behavior in rats

10. **Carranza-Jasso R, Rivera MC, Carranza-Jasso L** Development of an HTML5-Based Task for the Study of Pavlovian and Instrumental Conditioning in Humans

11. **Collins AL, Aitken TJ, Casillan AT, Lambing H, Greenfield V, Ostlund SB, Wassum KM** Pause, Collaborate, and Listen: The interaction of nucleus accumbens core acetylcholine and dopamine in cue-motivated reward seeking

12. **Colon LM, Poulos AM** Time and sex dependent contextual processing within the hippocampus

13. **Odynocki N, Poulos AM** Pavlovian Fear Conditioning: The Behavioral and Neuroanatomical Effects of Recent and Remote Memory in Between- and Within-Subject Designs

14. **de Solis CA, Holehonnur R, Kim LJ, Jones LE, Daison DK, Vuong DT, Khakoo SF, Ploski JE** Overexpression of GluN2A or GluN2B within neurons of the mouse basal and lateral amygdala alters amygdala dependent mnemonic processing

15. **DeAngeli ND, Fournier DI, Todd TP, Bucci DJ** Disambiguating the contribution of parahippocampal regions to retrieval and extinction of recent and remote fear memories

16. **Della Valle RB, Chamness M, Moulton E, Knox D** Single prolonged stress enhances Akt signaling in the amygdala during fear memory formation

17. **Doan C, Vinnick M, Freestone DM** Mice weigh time intervals more than reward magnitudes

18. **Freestone DM, Donskoy B, Benson-Xu E, Sari D, Early K, Myers KP** Rats do not adjust their timing precision (but they can)

19. **Dutta S, Gilman TL, Fouty J, Cecil C, Adkins S, Jasnow AM** Role of the nucleus accumbens in cued fear extinction

20. **Eddy MC, Huszár R, Bucci DJ** The retrosplenial cortex and its connections with the medial prefrontal cortex are crucial for inhibitory learning and behavior.

21. **Ellis AS, Bongiovanni A, Bhakta S, Knouse M, Thomas A, Peer K, Wimmer ME** Paternal morphine exposure causes maladaptive behavior in male progeny

22. **Farley SJ, Albazboz H, Freeman JH** Modulating Acquisition of Delay Eyeblink Conditioning with Optogenetic Excitation and Inhibition of the Rat Amygdala Central Nucleus

23. **Ferrara NC, Cullen PK, Pullins SE, Helmstetter FJ** Thalamic inputs onto the amygdala regulate fear memory retrieval

24. **Fink AJP*, Schoonover CE*, Axel R** A naturalistic assay for measuring behavioral responses to aversive stimuli at millisecond timescale

25. **Fisher H, Greig S, Weston A, Pickens CL** Three injections of anesthetic ketamine improve performance in a go/no-go reversal learning task and alter parvalbumin-positive neuronal expression in rats

26. **Fraser KM Janak PH** Feature-positive occasion setting is dependent upon neuronal activity in the basolateral amygdala

27. **Gardner MP, Conroy JS, Styer CV, Schoenbaum G** Lateral orbitofrontal cortex inactivation dissociates devaluation-sensitive behavior and economic choice

28. **Ghirlanda S, Enquist M** On the role of responses in Pavlovian conditioning

29. **Giustino TF, Fitzgerald PJ, Maren S** Locus coeruleus activation drives prelimbic cortical firing and induces relapse of extinguished fear

30. **Goode TD, Acca GM, Maren S** The bed nucleus of the stria terminalis mediates expression of fear to temporally unpredictable threats

31. **Ressler RL, Goode TD, Maren S** Inhibition of protein synthesis in the dorsal hippocampus prevents reconsolidation of a covertly retrieved fear memory

32. **Ramanathan KR, Jin J, Maren S** Prefrontal-reuniens projections contribute to the acquisition and expression of fear extinction

33. **Goodfellow MJ, Shin Y, Lindquist DH** Early developmental ethanol exposure increases IL-1 receptor signaling and diminishes long-term memory consolidation in male juvenile rats.

34. **Gould TJ, Kutlu MG, Parikh V** Paternal Nicotine Exposure Alters Generational Fear Conditioning and Hippocampal Cholinergic Function

35. **Gutierrez AG, Sunsay C** Pavlovian conditioning of social exploration to a transient cue

36. **Handy JD, Avcu P, Ko N, Ortiz A, Doria MJ, Servatius RJ** Facilitated Eyeblink Conditioning and Delayed Extinction in Active Duty Military Expressing Posttraumatic Stress Disorder Symptoms

37. **Johnson AW** The influence of CS-US interval and US density on the expression of cue-potentiated feeding

38. **Kalmbach AS, Simpson EH, Balsam PD** Reward availability in the presence and absence of conditioned inhibitory cues is encoded by dopamine in the ventral striatum

39. **Kaminer J, Diaz-Acevedo MA, Espinoza DG, Tepper JM, Koós T, Shiflett MW** Effects of Striatal TH-Interneuron Lesions on Goal-Directed Instrumental Behavior

40. **Kass MD, McGann JP** Persistent, generalized hypersensitivity of olfactory bulb interneurons after olfactory fear generalization

41. **Keiflin R, Pribut HJ, Shah NB, Janak PH** Dissociable Roles of Ventral Tegmental and Substantia Nigra Dopamine Neurons in Reinforcement Learning

42. **Kenney L, Nussbaum H, Gotthard GH** Reminder Treatment Effective for Reversal of Cycloheximide-Induced Amnesia in Rats

43. **Kirry AJ, Herbst MR, Twining RC, Gilmartin MR** Direct communication between the medial prefrontal cortex and the basolateral amygdala in the formation of a trace fear memory.

44. **Latsko MS, Jasnow AJ** Corticosterone ameliorates the adult social behavior defisits caused by periadolescent social defeat

45. **Lay BPP, Nicolossi M, Usypchuk A, Esber G, Iordanova MD** Infralimbic cortex regulation of overexpectation and extinction

46. **LeCocq MR, Lahlou S, Chahine M, Padillo LN, Chaudhri N** Reinstatement and spontaneous recovery of Pavlovian-conditioned alcohol-seeking behaviour in rats

47. **Ludwig RJ, Kwon KY, Welch MG** Pavlovian Conditioning: It's MORE than you think it is

48. **Mahmud A, Cossette M-P, Lay BPP, Esber G, Iordanova M** VTA Dopamine Transients Reduce Prediction Error about Aversive Outcomes

49. **Mueller I, Brinkman AL, Sangha S** Juvenile pre-exposure to fear, safety or reward cues affects discriminatory conditioning in adulthood

50. **Ng KH, Sangha S** Neuronal encoding of fear, safety, and reward cue discrimination in the infralimbic cortex

51. **Norris MR, Greiner E, Mueller I, Ng KH, Sangha S** Sex differences in suppression of conditioned fear during a safety cue in a fear-safety-reward cue discrimination task

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

1. **Luyten L, Beckers T** A preregistered, direct replication attempt of the retrieval-extinction effect in cued fear conditioning in rats

2. **Luyten L, Luyck K, Gabriëls L, Nuttin B** Electrical stimulation in the bed nucleus of the stria terminalis reduces anxiety in rats and patients

3. **Malvaez M, Shieh C, Murphy MD, Greenfield VY, Monbouquette HG, Wassum KM** Amygdala-cortical circuits in reward value encoding and retrieval

4. **Meyer HC, Amelio P, Lee FS** Influences of adolescent cued and contextual fear representations on safety learning

5. **Miller DP, Latham H, Cook-Snyder DR, Servatius RJ** Partially reinforced signaled lever press conditioning reveals differences in the expectation versus the presence of shock in behaviorally inhibited Wistar-Kyoto rats compared to Sprague Dawley rats

6. **Miller LA, Heroux NA, Stanton ME** Mechanisms of contextual fear conditioning in pre-weanling and adolescent rats

7. **Heroux NA, Robinson-Drummer PA, Rosen JB, Stanton, ME** Neonatal ethanol exposure impairs the context preexposure facilitation effect (CPFE) in adolescent rats: Acquisition, retention, and reinforcement effects

8. **Robinson-Drummer PA, Long VS, Stanton ME** Evidence of NMDA-independent acquisition of context memory in adolescent rats

9. **Mohammadmirzaei N, Della Valle R, Knox D** Traumatic stress alters neural activity during fear and extinction learning and memory in non-relay thalamic nuclei

10. **Moulton E, Chamness M, Knox D** Examining the effects of single prolonged stress on glucocorticoid receptor internalization in emotional circuits in the brain

11. **Myers KP, Brunick AJ, Gerber RB, Kim ES** The 'cue ubiquity paradox' in overeating: conditioned food seeking elicited by unreliable food cues in lean and obese rats

12. **Nasser HM, Lesser EN, Lafferty DS, Bacharach SZ, Calu DJ** Role of dissociable basolateral amygdala pathways in sign- and goal-tracking behaviors

13. **Nelson B, Nelson E, Horenstein K, Edwards A, Lipatova O, Campolattaro MM** The impact of fornix lesions on tone-on-trace and tone-off-delay eyeblink conditioning

14. **Opendak M, Perry R, Diaz-Mataix L, Santini E, Doyere V, Klann E, LeDoux JE, Sullivan RM** Maternal gating of infant memory consolidation via distinct molecular events in the amygdala

15. **Ortiz S, Latkso MS, Jasnow AM** A novel neural circuit promoting fear generalization

16. **Pajser A, Gaeddert B, Fisher H, Long C, Kallenberger P, Limoges A, Pickens CL** Operant overtraining increases infralimbic activity in the fear incubation task

17. **Pan PL, Keiser AA, Tronson NC** Context fear memory retrieval induces sex-specific recruitment of the ventral hippocampus

18. **Keiser AA, Pan PL, Tronson NC** Sex-specific decrease of remote context fear memory

19. **Parsons RG, Lee J, Russo AS** Mechanisms by which prior fear conditioning facilitates subsequent fear learning

20. **Polack CW, Craddock P, Wasserman JS, Miller RR** Associative chains support second-order conditioning in humans

21. **Pullins SE, Cullen PK, Ferrara NC, Helmstetter FJ** Contributions of the retrosplenial cortex to event-related and contextual fear memory formation in trace fear conditioning

22. **Ramsaran AI, Nath M, Ahmed M, Josselyn SA, Frankland PW** Perineuronal nets regulate hippocampal memory formation and specificity

23. **Rankin CH, McDiarmid TA** Identifying the behavioural function of genes and gene networks associated with Autism Spectrum Disorder using C. elegans

24. **Reis DS, Helmstetter, FJ** Sex differences in differential fear cnditioning during the acquisition and consoidation of learned safety

25. **Reverte I, Jou C, Shur A, Flores L, Iordanova M, Esber G** A self-initiated Pavlovian procedure for in-vivo electrophysiology recording

26. **Rice BA, Eaton SE, Prendergast MA, Akins CK** A glucocorticoid receptor antagonist reduces sign-tracking behavior in male Japanese quail

27. **Richard JM, Stout N, Acs D, Janak PH** Ventral pallidal encoding of reward seeking depends on the underlying associative structure

28. **Sevenster D, Haesen K, Vervliet B, Kindt M, D'Hooge R** Prevention and treatment strategies for enhanced contextual generalization

29. **Shang A, Bylipudi S, Bieszczad KM** A role for HDAC3 in the specificity of memory consolidation

30. **Sharp JL, Miller-Cahill ME, Fountain SB, Riccio DC** Serial Pattern Retention in Male and Female Rats

31. **Sharpe MJ, Mueller LE, Batchelor HM, Schoenbaum G** Lateral Hypothalamic GABAergic neurons actively oppose learning about the general structure of our environment in favor of cues most proximal to reward.

32. **Shipman ML, Trask S, Bouton ME, Green JT** Inactivation of prelimbic and infralimbic cortex respectively affect expression of minimally-trained and extensively-trained goal-directed actions

33. **Freestone DM, Donskoy B, Benson-Xu E, Sari D, Early K, Myers KP** Rats do not adjust their timing precision (but they can)

34. **Spiegler KM, Smith IM, Fortress AM, Pang KCH** Persistent avoidance in anxiety-vulnerable Wistar-Kyoto rats: The role of danger and safety signals

35. **Starosta S, Frey M, Kepecs A** Behavioral algorithms and neural substrates of stay-or-leave decisions

36. **Steele CC, Davis IR, Kirkpatrick K** The effect of dietary exposure on impulsive choice in male and female rats: An investigation of individual differences

37. **Steinfeld MR, Thrailkill EA, Bouton ME** Extinction of procurement prevents renewal of consumption when an extinguished consumption response is returned to a heterogeneous chain

38. **Takahashi YK, Batchelor HM, Liu B, Khanna A, Morales M, Schoenbaum G** Dopamine neurons respond to errors in the prediction of sensory features of expected rewards

39. **Thrailkill EA, Trask S, Bouton, ME** Can discriminated operants become habits?

40. **Trask, S, Keim, CL, Bouton, ME** Factors that Encourage Generalization from Extinction to Test Reduce Resurgence of an Extinguished Operant Response

41. **Twining RC, Herbst MR, Kirry AJ, Lepak K, Durigan D, Gilmarti MR** Selective silencing of ventral hippocampal inputs to the prefrontal cortex during trace fear conditioning impairs contextual memory.

42. **Voulo ME, Parsons RG** Response-specific sex difference in the retention of fear extinction

43. **Russo AS, Parsons RG** Activity of the Mitogen-Activated Protein Kinase in the amygdala and prefrontal cortex associated with individual variation of fear extinction in rats

44. **Whitlow JW, Ferris N** On the representation of novelty in associative learning

45. **Wiersielis K, Ceretti A, Salvatore M, Lefebo H, Famularo S, Cantoral V, Jang H, Bangasser D** Corticotropin releasing factor in the medial septum impairs spatial learning in rats

46. **Williams AR, Lattal KM** The Behavioral and Neurobiological Characteristics of Rapid Reacquisition of Conditioned Fear following Extinction

47. **Marton TM, Han E, Shuler MGH** Animals Shouldn't and Don't Use A Temporal Difference Reinforcement Algorithm to Learn How to Spend Time: A Comparison to Novel Alternative Reward-Optimizing Algorithms.

48. **Wilson WJ** Pavlov's 1923 Visit to Battle Creek

49. **Yuan X, Marton T, Shuler MGH** A New Behavioral Framework for Testing Novel Value Variables Enabling Temporal Decision-Making

50. **Zhou J, Stalnaker T, Ramus S, Schoenbaum G** Orbitofrontal ensembles encode current state or "place" within an odor sequence task

51. **Anderson LC, Petrovich GD** DREADD manipulations of ventromedial prefrontal cortex neurons during renewal of Pavlovian conditioned responding to food cues in male and female

rats

Abstracts

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

Adkins JM, Gilman TL, Dutta Sohini, Jasnow AM *Activation of Corticotropin-releasing factor (CRF) Neurons within the Central Nucleus of the Amygdala Reduces Fear Expression in Mice*
Corticotropin-releasing factor (CRF) is a stress-related neuropeptide expressed by neurons within several regions throughout the brain. One of the regions with intense CRF expression, the central nucleus of the amygdala (CeA), is critically important for encoding and regulating fear behavior. Previously, using a CRF-NR1 knockout mouse we have shown that reduced NMDA-mediated activation of CRF-expressing (CRF+) neurons results in exaggerated fear responses to fearful and non-fearful cues. To directly investigate the impact of activating CeA CRF+ neurons on fear behaviors, we used optogenetics and designer receptors exclusively activated by designer drugs (DREADDs) to selectively activate or inhibit CRF+ neurons of the CeA during fear testing. Adult male and female transgenic mice expressing Cre under CRF promoter control were infused with Cre-dependent virus coding for the DREADD (hM3D), or a Cre-dependent channelrhodopsin (ChR2) virus into the lateral portion of the CeA (CeL), where majority of the CRF-expressing CeA neurons are located. Mice underwent contextual or cued fear training 3 weeks later. Specific activation of CeL CRF+ neurons strongly reduced cued and context fear expression in mice. Given the projections of CRF neurons in the CeL, we hypothesized the fear reducing effects were due to either GABA or CRF release in the CeM. Infusion of the CRFR1 antagonist (Antalarmin) locally into the CeM immediately before DREAD activation of CeL CRF+ neurons did not abrogate the CRF+-mediated

reduction in fear. However, infusion of the GABAA receptor agonist (muscimol) locally within the CeM significantly reduced fear, similar to CRF+ neuron activation. Therefore, we determined the reduction of fear following CRF+ neuron activation is likely mediated by local GABA release onto CeM neurons. Overall, we found that activating CeL CRF+neurons dramatically reduced fear expression, and that it is likely occurring through GABA release in the CeM. These data suggest that these neurons may be critical in regulating pathological fear and may provide a potential mechanism for sex differences in fear-related and anxiety disorders in humans.

Akdogan B, Gallistel CR, Wanar A, Gersten BK, Balsam PD *Temporal Representations in the Duration Discrimination Task*
Temporal information-processing is critical for adaptive behavior and goal-directed action. It is thus crucial to understand how the temporal distance between behaviorally relevant events is encoded to guide behavior. However, research on the nature of temporal representations has yielded mixed findings as to whether organisms utilize relative versus absolute judgments of time intervals. To address this fundamental question about the timing mechanism, we tested mice in a duration discrimination procedure in which they learned to correctly categorize tones of different durations as short or long. After being trained on a pair of target intervals the mice transferred to conditions in which target intervals and corresponding response locations were systematically manipulated. Specifically, response and/or durations of cues were switched in different experimental phases so that either the relative or absolute mapping remained constant. The adjustments of duration discrimination performance to these changes in temporal and spatial contingencies were examined with respect to a variety of indices of timing behavior including acquisition, learning rates, temporal sensitivity, and response times associated with short and long categorizations. The findings collectively revealed that although mice encode the absolute relation between durations, the transfer occurred most readily when the relative mapping between durations and corresponding response locations was maintained. The findings indicate

that the default temporal representations in a duration discrimination task rely heavily on relative rather than the absolute coding of time intervals.

Alfei JM, Ferrer Monti RI, Luyten L, De Bundel D, Molina VA, Beckers T *Generalization and post-retrieval amnesia*
Threat memories can become sensitive to interference or disruption upon their retrieval, provided that retrieval is accompanied by an appropriate degree of prediction error (Beckers & Kindt, 2017; Exton-McGuinness et al., 2014). Of note, similar conditions can be said to govern the extinction of conditioned defensive responses: CS-elicited memory retrieval accompanied by negative prediction error. In a series of experiments, we set out to test whether those two conditions are jointly sufficient for inducing sensitivity to post-retrieval amnesia. We find that in specific circumstances, solid memory retrieval (as evidenced by strong conditioned responding) accompanied by optimal prediction error does not yield sensitivity to generalized drug-induced post-retrieval amnesia, in a way that is problematic for reconsolidation blockade as well as state dependency accounts of post-retrieval amnesia. ERC Consolidator Grant 648176

Alfei JM, Ferrer-Monti RI, Mugnaini M, Bueno AM, Beckers T, Urcelay GP, Molina VA *A comparison of behavioral and pharmacological interventions to attenuate reactivated fear memories*
Two experiments using rats in a contextual fear memory preparation compared two approaches to reduce conditioned fear: (1) pharmacological reconsolidation blockade and (2) reactivation-plus-extinction training. In Experiment 1, we explored different combinations of reactivati plus-extinction parameters to reduce conditioned fear and attenuate reacquisition. In Experiment 2, memory reactivation was followed by extinction training or administration of midazolam (MDZ) (vs. vehicle) to reduce conditioned fear and attenuate spontaneous recovery. We found both treatments to be equally effective in both experiments. This study suggests that parameters leading to memory destabilization during reactivation are critical to observe long-lasting effects of

MDZ or reactivation plus extinction.

Allen MT, Blankenship MR, Servatius RJ *The Distressed (Type D) Personality Factor of Social Inhibition, but Not Negative Affectivity, Enhances Eyeblink Conditioning: Further Support for a Learning Diathesis Model of Anxiety Disorders*
Recent work has focused on a learning diathesis model in which a temperamental factor may influence associative learning and in turn increase risk for the development of anxiety disorders. We have found in a series of studies that individuals self-reporting high levels of behavioral inhibition (BI) exhibit enhanced acquisition of conditioned eyeblinks. In the work reported here, the exploration of how personality can influence anxiety vulnerability through associative learning was extended to include distressed (Type D) personality. Type D personality is measured with the DS14 scale which includes two subscales: negative affect (NA) and social inhibition (SI). Based on prior work, we hypothesized that SI, but not NA, would be related to enhanced eyeblink conditioning. Sixty participants completed personality inventories including the Adult Measure of Behavioral Inhibition (AMBI) and DS14. All participants received 60 acquisition trials with a 500 ms, 1000 Hz, tone CS and a 50 ms, 5 psi corneal air puff US. Behaviorally inhibited individuals acquired conditioned eyeblinks at a faster rate than non-inhibited individuals ($p < 0.05$). Socially inhibited individuals exhibited enhanced eyeblink conditioning as compared to non- inhibited individuals ($p < 0.05$), but there was no effect of NA on eyeblink conditioning. Personality factors now including social inhibition as well as behavioral inhibition can be used to differentiate fast and slow learners supporting the utility of eyeblink conditioning as a behavioral measure for assessing anxiety vulnerability. University of Northern Colorado and the Stress and Motivated Behavior Institute

Anderson LC, Petrovich GD *DREADD manipulations of ventromedial prefrontal cortex neurons during renewal of Pavlovian conditioned responding to food cues in male and female rats*
Cues associated with food can stimulate appetite and food consump-

tion independently of hunger. Renewal, or reinstatement, of responding to food cues after extinction may explain the inability to resist palatable foods and change maladaptive eating habits. Recently, we found sex differences in context-dependent renewal of responding to extinguished Pavlovian food cues and differential recruitment within the ventromedial prefrontal cortex (vmPFC). Male rats exhibited renewal of responding and had higher Fos induction within the vmPFC compared to a control group, while females failed to show renewal of responding and had lower Fos induction within the vmPFC compared to a control group. Here, we used DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) to silence vmPFC neurons in males (Experiment 1) and to stimulate the vmPFC in females (Experiment 2) during renewal. In Experiment 1, male, Long-Evans rats received bilateral injections into the vmPFC of a viral vector containing the gene for a synthetic inhibitory G-protein-coupled receptor (AAV5-hSyn-HA-hM4D-IRES-mCitrine) or a control viral vector (AAV5-hSyn-EGFP). After recovery rats were trained in a within-subjects Pavlovian context-dependent renewal protocol. Rats were trained to associate a tone (conditioned stimulus, CS) with food (unconditioned stimulus) in acquisition sessions in Context A. Acquisition was followed by extinction sessions with CS-only presentations in Context B. Rats were tested for renewal of responding with CS-only presentations in Context A and Context B, counterbalanced for order, on separate days. 30 minutes prior to each test, rats were injected with clozapine N-oxide (CNO, biologically inert, DREADD-selective ligand; 3mg/kg, i.p.) or vehicle. Rats either received CNO on both days or vehicle on both days. The resulting groups were: DREADD+CNO, DREADD+Vehicle, and Control Virus+CNO. The measure of learning was an increase in the expression of food cup behavior (conditioned response, CR) during CSs. Renewal of responding was determined by significantly higher CRs in the acquisition context (Context A) compared to the extinction context (Context B). On tests, the DREADD+CNO group failed to show renewal responding with similar low responding to CS in both contexts, while DREADD+Vehicle and Control+CNO groups showed renewal responding with higher in-

duction of CR to the CS in the acquisition context. In Experiment 2, female rats received a viral vector containing the gene for a synthetic stimulatory G-protein-coupled receptor (AAV5-hSyn-HA-hM3D-IRES-mCitrine) and were trained in the same behavioral procedure as males. At test, the DREADD+CNO group had higher induction of CR to the CS in the acquisition context, while control groups had similar responding to the CS in both contexts. Therefore, silencing vmPFC neurons in males disrupted renewal of food cup responding while exciting vmPFC neurons in females induced renewal of food cup responding. These results demonstrate the vmPFC activation is critical during renewal of responding to food cues and a site of sex differences. NIH Grant R01DK085721

Arnaudova I, Beckers T *Generalization of extinction: Examining fear recovery to conditioned and generalization stimuli following extinction with conditioned or generalization stimuli*
Traditionally, exposure treatment has been modeled in the laboratory by extinction of conditioned stimuli (CS). However, in real life, it is highly unlikely that individuals seeking therapy can be exposed to the original stimuli present at the time of fear memory formation (i.e., CSs). It is more likely that they will be exposed to some form of generalization stimuli (GSs), which share resemblance with the original CSs. Yet, GS extinction is rarely studied in the lab. In two studies, participants received differential fear conditioning followed by extinction treatment that involved 1) the actual CSs, 2) a pair of GSs or 3) multiple GSs. Two different shapes (a circle and a square) were used as CSs. GSs were different gray-scale versions of the CSs. At test, fear responding was measured to either the CSs (Experiment 1), to GSs on the same perceptual continuum, or to GSs of a different kind (shape words, Experiment 2). Avoidance responding was also assessed. Differences were observed during extinction and at test, in fear recovery to the various stimuli, as well as avoidance. Theoretical and clinical implications of the findings will be discussed.

Bacharach SZ, Nasser HM, Dantrassy HM, Zlebnik NE, Cheer JF,

Calu DJ *CB1 receptor signaling enhances stimulus value attribution in Pavlovian and instrumental settings*

Prior studies suggest that dopamine (DA) in the nucleus accumbens (NAc) plays a time limited role in driving appetitive approach behavior of sign-, but not goal-trackers. Endocannabinoids (EC) are critical gatekeepers of dopaminergic signaling and antagonists of the cannabinoid-1 (CB1) receptor alter DA dynamics in the NAc to influence cue-motivated behavior in instrumental procedures that resemble Pavlovian lever autoshaping. Here, we investigate whether systemic CB1 receptor blockade during early and late phases of Pavlovian lever autoshaping mimics the effects of DA antagonists on sign-tracking but not goal-tracking. Previous studies using retractable lever cues, under either Pavlovian or instrumental contingencies, similarly observe cue-evoked fluctuations of DA in the NAc. Therefore, we sought to determine the extent to which CB1 receptor signaling is involved in Pavlovian versus instrumental processes. We first tested the hypothesis that systemic injections of CB1 receptor inverse agonist, rimonabant (SR141716A), would block sign-, but not goal- tracking behaviors. We trained male and female rats in Pavlovian lever autoshaping sessions to determine their sign-tracking (ST), goal-tracking (GT) or intermediate-tracking (INT) phenotype. We tested rats with systemic injections of rimonabant (0, 1, 3 mg/kg) during early (sessions 5-7) and late (sessions 15-17) reinforced Pavlovian lever autoshaping sessions. In early Pavlovian lever autoshaping sessions, rimonabant dose-dependently decreased both lever and food cup directed behaviors. With continued training in lever autoshaping many previously GT and INT rats shifted towards lever-directed behaviors, which continued to be dose-dependently sensitive to the effects of rimonabant, particularly for extreme sign-trackers but not intermediates or rats that shifted towards sign-tracking over time. Next we investigated the extent to which CB-1 receptor signaling mediates performance in cued-instrumental procedures. We first isolated the instrumental contingency by training the same group of ST, GT, and INT rats to acquire a cued-instrumental nosepoke response with an ITI identical to previous reward history and then tested the effect of

rimonabant on instrumental performance. Rimonabant did not affect the instrumental performance under long ITI conditions that limit the attribution of value to the instrumental action. We then reduced the duration of the inter-trial interval (ITI) and tested the effect of rimonabant on instrumental performance. Rimonbant impaired instrumental performance under short ITI conditions that theoretically promote enhanced incentive value of the instrumental action. Together, our results suggest that CB1 receptor signaling enhances a predictive cue's ability to initiate and invigorate conditioned responding, regardless of whether it is to support Pavlovian approach or instrumental action.

Bailey C, Schnegelsiepen A, Stuebing S, Marshall AT, Peterson JR, Kirkpatrick K *Generalizability of Fixed-Interval Intervention on Impulsive Choice in Rats*
Impulsive choice is the desire to choose a less valuable reward occurring sooner over waiting for a higher value reward occurring later. Due to the importance of timing processes in the delay aspects of impulsive choice, time-based interventions have been developed to decrease impulsive choice. Previous work has shown that a fixed-interval intervention decreases impulsive choice when the rats were tested on a single choice task and that those effects were long lasting. The goal of this experiment was to determine if the effects of the fixed-interval intervention generalize to multiple choice tasks. The results suggest that the intervention generalizes across choice tasks, but the testing order affected the expression of the intervention effects.

Bangasser, DA *Stress regulation of sustained attention*
Attention impairments are reported in patients with disorders ranging from schizophrenia to attention deficit hyperactivity disorder. Another shared feature of these disorders is that stress worsens their symptoms and progression. Although stress can disrupt attention, the neurobiological mechanisms by which this occurs remain largely unknown. My laboratory is beginning to address this gap by investigating in male and female rats how stress alters sustained attention, the ability to detect intermittent and unpredictable events over

time. To this end, we use a sustained attention task (SAT), where rats are trained to distinguish signal trials, in which a brief light is presented, from non-signal trials. We found that central administration of the stress-neuropeptide, corticotropin releasing factor (CRF), dose-dependently impaired performance on SAT in both sexes. Interestingly, the magnitude of the attention deficit changed across the estrous cycle of female rats, such that CRF impaired attention when ovarian hormone levels were low, but not when they were high. This result suggests that ovarian hormones protect females from CRF-induced attentional impairments. We are now exploring where in the brain CRF is working to modulate SAT and preliminary data suggest that CRF can directly regulate the nucleus basalis of Meynert (NBM) within the cholinergic basal forebrain to impair aspects of sustained attention. A complementary line of work is finding that chronic variable stress impairs sustained attention in rats. Preliminary data are also revealing that chronic variable stress causes the remodeling of dendrites of cholinergic neurons in the NBM. Because these neurons are known to mediate SAT, this stress-induced remodeling could underlie impaired attention following chronic stress. Collectively, these studies suggest that stress can impair sustained attention via CRF and that chronic stress can induce structural plasticity in cholinergic neurons. Developing a better understanding of these processes may lead to the identification of new targets that can be manipulated therapeutically to improve attention in stressed patients with a variety of disorders. This work was supported by MH092438 and NSF IOS-1552416 to D.A.B.

Bath KG, Manzano-Nieves G, Bravo M, Johnsen A *ELS is associated with precocious amygdala development and an unexpected dip in threat-associated freezing*

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 ma-

ternal 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 dip in freezing behavior at 21 days of age. This dip in freezing behavior was associated with a precocious maturation and spike in the 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 took advantage of optogenetic techniques 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. These results have implications for understanding the effects of ELS on the ontogeny of circuit development and its impact on the development and expression of fear associated responding. Brown Institute for Brain Sciences, Norman Prince Neuroscience Institute

Beaver J, Dutta S, Gilman TL, Cecil C, Adkins JM, Jasnow AM
Thy1 Neuron Activation in BLA Promotes Fear Inhibition and Reduces Defeat-Induced Social Inhibition
Thy1 neurons are a subset of glutamatergic neurons found throughout the brain, including in the basolateral amygdala (BLA). Previously we have demonstrated that optogenetic activation of BLA Thy1 neurons attenuates cued fear learning and enhances cued extinction learning, suggesting that BLA Thy1 neuron activity promotes inhibition of fear. To further investigate these findings, we employed designer receptors exclusively activated by designer drugs (DREADDs) to selectively activate BLA Thy1 neurons. Adult male Thy1-Cre mice were stereotaxically infused with a Cre-dependent virus coding for the activational (Gs) DREADD rM3D. This permitted selective activation of only BLA Thy1 neurons during either a passive avoidance paradigm to investigate contextual fear processing, or a social defeat paradigm to examine defeat-induced social withdrawal. For passive

avoidance, BLA Thy1 neurons were activated at one of following time-points: after initial training, after extinction training, after reactivation or before testing. With respect to social defeat stress, BLA Thy1 neurons were activated either after each of the two defeat sessions, or before social interaction testing. We found that activating BLA Thy1 neurons after initial extinction trainings and reactivation resulted in decreased expression of fear 48 h later, whereas there was no effect when these neurons were activated 30 min before testing. Further, BLA Thy1 neuron activation was effective in reducing fear following a 10-min extinction training session, but not after a 5 min session, suggesting that a threshold of learning must be satisfied in order for these neurons to successfully promote fear inhibition. In contrast, activating BLA Thy1 neurons after social defeat stress did not affect social interaction. However, activating these neurons 30 min prior to testing increased social investigation selectively in defeated animals, without influence social interaction of non-defeated control mice. Overall, these findings indicate that BLA Thy1 neurons inhibit fear behavior and defeat-induced social avoidance possibly through distinct mechanisms. Future work will be directed at dissecting the downstream brain regions responsible for the immediate effects of BLA Thy1 neuron activation on reducing the expression of social avoidance and the influence on fear and extinction learning.

Ben-Ami Bartal I, Long K, Keltner D, Kaufer D *Neural substrates of pro-social behavior in rats*

Helping a conspecific in distress is a complex behavior that results from a response to cues of distress from an animal in need. What happens in the brain from the moment these cues are perceived that lead up to a behavioral decision to approach? I am addressing this question with a rodent model of helping behavior in which rats get the opportunity to help other rats by releasing them from a trap. Using immunohistochemistry across the whole brain, we have constructed a connectome of helper rats. We have further explored the neural activity of these animals in-vivo using fiber photometry. I will discuss the networks important for helping specifically, and focus on the dif-

ferent response in non-empathic situations, ie. When rats are paired with a trapped rat of a different strain.

Bouton ME *Contextual Control of Retroactive Inhibition in Instrumental Learning*
Previous research in Pavlovian learning suggests that retroactive and proactive interference often depend on retrieval processes that are controlled by the context. For example, in extinction, counterconditioning, discrimination reversal, and latent inhibition, the interference one observes in Phase 1 or Phase 2 depends at least partly on which of two available associations (or CS "meanings") the context retrieves. As noted in a review by Bouton (1993), this perspective is consistent with what was known about the effects of context and time (the "temporal context") on performance in the various interference paradigms. Thus, the evidence supported (1.) a very general view of interference, and (2.) a very general view of "context." This talk will focus on research that has extended the analysis to instrumental (operant) learning. Context again plays a general role in retroactive interference. For example, after extinction, omission learning, or punishment, a change of context can result in the renewal (relapse) of the suppressed response. Moreover, many kinds of stimuli or events can play the role of context, including apparatus, time, deprivation state, stress state, recent reinforcers, and previous responses. In instrumental interference, the evidence suggests that the animal learns to inhibit a specific response in a specific context.

Brown LA, Foa EB *Prolonged Exposure Therapy in the Recovery from Posttraumatic Stress Disorder*
Up to 20% of women who experience randomly selected sexual assaults meet diagnostic criteria for posttraumatic stress disorder (PTSD). Models of fear conditioning and extinction provide useful experimental analogues for PTSD and have been leveraged in the treatment of PTSD for survivors of violence. In this presentation, we will review findings from both naturalistic and randomized controlled trials (RCT) on the association between PTSD and deleterious health con-

sequences including suicide risk, and describe how Prolonged Exposure therapy (PE) promotes recovery from PTSD and reduction of suicide risk through enhancing extinction learning. We will begin by describing how principles of extinction learning are enhanced in PE by in vivo exposure and imaginal exposure practice, as well as how exposure promotes violation of negative trauma-related expectancies, thereby reducing conditioned fear responses. We will then describe evidence for the efficacy of PE in two studies implemented in female survivors of violence. The first compared the efficacy of PE relative to supportive counseling in adult female survivors of violence through partnership with Women Organized Against Rape (WOAR) in Philadelphia, PA. The second compared the efficacy of PE relative to supportive counseling in adolescent survivors of sexual violence. Across both trials, significant reductions in PTSD and related conditions were found and will be reviewed. We will conclude by discussing strategies to enhance PE through principles derived from the extinction and inhibitory learning literature.

Callaghan BL, Fields A, Gabard-Durnam LJ, Gee DG, Caldera C, Humphreys KL, Goff B, Flannery J, Telzer EH, Shapiro M, Tottenham N *Brain Bugs - Understanding the role of the gut microbiome in stress, learning, and mental health*

The microbiome is increasingly recognized as important for brain function. In particular, rodent models have shown that microorganisms residing in the gut influence emotional behavior and are linked to altered brain states, especially in emotion-related regions (e.g., prefrontal cortex and hippocampus). Rodent models also demonstrate that both brain and the microbiome are regulated by environmental events, and are maximally responsive to those events in early life. Using a cross-species translational model, we explore the role of the microbiome in brain and behavior changes that emerge following early adversity exposure. In rat pups, we show that fear behavior is altered following early adversity, and that these behavioral changes can be ameliorated by manipulating the gastrointestinal microbiome. In an effort to translate those findings to developing hu-

man populations, we have performed a proof-of concept study, linking early environments to microbiome and brain (using functional magnetic resonance imaging; fMRI). We show that early exposure to adverse caregiving is associated with lasting changes in the gastrointestinal microbiome (even decades after adversity has ended), and that such microbiome differences are associated with altered reactivity and connectivity in threat circuitry (i.e., in amygdala, prefrontal cortex, and hippocampus). Moreover, we show that several of these brain changes are associated with anxiety in developing youth. These data provide firm proof of concept for the importance of adversity-associated microbes in brain function and anxiety across development, supporting the need to enhance research attention in this area. This research was supported by a a National Institute of Mental Health Grant (R01MH091864) to NT, a Dana Foundation grant to NT, and a National Health and Medical Research Council Early Career Fellowship to BC, and a Sackler Parent Infant Project Fellowship to BC.

Carranza-Jasso R, Rivera M C, Carranza-Jasso L. *Development of an HTML5-Based Task for the Study of Pavlovian and Instrumental Conditioning in Humans*

Pavlovian and instrumental conditioning have been widely used to study multiple behavioral phenomena, including effects of response recovery, in human and non-human animals (Bouton, Trask, & Carranza-Jasso, 2016; Cartoni, Balleine, & Baldassarre, 2016; Delamater, 2012; Hardy, Mitchell, Seabrooke, & Hogarth, 2017; Tantot et al., 2017; Trask, Thrailkill, & Bouton, 2017; Valenchon, Levy, Moussu, & Lansade, 2017). In order to study human behavior, some tasks have been proposed (LeÃşn, Abad, & Rosas, 2015; Nelson, Navarro, & del Carmen Sanjuan, 2014) but they require, either the use of specialized research software such as SuperLab Pro, or computers with specific hardware and software requirements, and both imply complicated installations and/or configurations. To provide an alternative to these research tools, we developed a simple and user-friendly, yet powerful and versatile HTML5-based task. This task allows the manipulation of four discrete stimuli, four outcome displays and seven dif-

ferent contexts, as well as the recording of four possible responses issued by participants. Also, two experiments were conducted to replicate contextual phenomena, previously reported in animal behavior, using human participants. The task recorded and retrieved reliable and consistent data, making it a resourceful and powerful research tool. These experiments were funded by the federal research grant PRODEP-DSA/103.5/16/10627, and by the institutional research grant UAA-PIPS17-1.

Cheng DT *Alcohol Effects on Behavior and Brain Function during Human Eyeblink Conditioning*

Excessive alcohol consumption can have a serious impact on both drinkers and developing fetuses, leading to general learning impairments, including severe conditioning deficits (Jacobson et al., 2008; McGlinchey-Berroth et al., 1995). One brain region targeted by heavy alcohol exposure is the cerebellum (Norman et al. 2009; Sullivan and Pfefferbaum, 2005), a structure that is critical for eyeblink classical conditioning. However, the neural mechanisms by which alcohol affects cerebellar-mediated associative learning remain largely unexplored in humans. We used functional magnetic resonance imaging (fMRI) to investigate neural changes in adults with alcohol use disorders (AUD) and children with fetal alcohol spectrum disorders (FASD) during delay eyeblink classical conditioning. Behavioral conditioning deficits were found in the AUD and FASD groups relative to healthy adults and children. Despite these learning impairments, the AUD and FASD groups showed greater activation in the cerebellar cortex, specifically lobule VI. Deep nuclei activity significantly correlated with conditioned responses in the healthy controls, but not the alcohol groups. These results suggest that key cerebellar structures supporting eyeblink conditioning may be functionally disorganized in the alcohol groups, and that increased activation may serve as a compensatory mechanism. These findings are also the first to characterize abnormalities in brain function associated with the behavioral conditioning deficits seen in adults with alcohol use disorders and children with prenatal alcohol exposure. NIH/NIAAA

Collins AL, Aitken TJ, Casillan AT, Lambing H, Greenfield V, Ostlund SB, Wassum KM *Pause, Collaborate, and Listen: The interaction of nucleus accumbens core acetylcholine and dopamine in cue-motivated reward seeking*

Reward-predictive environmental stimuli provide a major source of motivation for reward-seeking behaviors. Considerable evidence has implicated the nucleus accumbens core (NAc), and dopamine signaling therein, in the expression of a cue's motivational value, but additional NAc modulatory mechanisms likely also contribute. Among these, the cholinergic interneuron (CIN) system has emerged as a potential key player. However, little is known about how striatal acetylcholine regulates cue-motivated behavior. Therefore, we first assessed the function of NAc CINs in the ability of a reward-paired cue to invigorate reward-seeking actions by manipulating CIN activity during a test of Pavlovian-to-instrumental transfer (PIT). Optogenetic stimulation of CINs concurrent with reward cue presentation was found to abolish the normal invigorating influence of that cue over reward-seeking actions. Additionally, both optogenetic and chemogenetic inhibition of NAc CINs augmented this cue-motivated behavior. Local pharmacological manipulations identified nicotinic acetylcholine receptors as the mediator of this suppressive function of NAc CIN activity over cue-motivated behavior; inactivation of NAc nicotinic receptors was found to augment cue-motivated behavior. Data collected ex vivo show that nicotinic receptors are located on striatal dopamine terminals where they can regulate release. So, we next coupled fast-scan cyclic voltammetry with local pharmacological manipulations to test the hypothesis that CIN activity functions to suppress cue-motivated behavior via nicotinic receptor-mediated regulation of dopamine release. In support of this, unilateral inactivation of NAc nicotinic receptors was found to augment cue-induced phasic dopamine release during PIT. These results reveal the functional significance of cholinergic terminal regulation of dopamine release and, collectively, demonstrate that activity in NAc CINs acts as a restrictive gate over the motivational influence of cues via terminal modulation

of dopamine release. Given NAc CIN activity has been shown to be regulated by satiety and other states that modulate the adaptive utility of cue responses, these data have implications for mental illnesses marked by dysregulated cue-induced motivation.

Colon LM, Poulos AM *Time and sex dependent contextual processing within the hippocampus*
Establishing a complete contextual representation of an environment places specific spatial-temporal processing demands on the mammalian hippocampus. Prior work indicates that these processing demands may be different in male and female animals. Here we examined in both male and female mice the relationship between the time dependent capacity to encode a contextual-spatial environment and the network activity of context fear related circuits including the hippocampus. Utilizing a contextual fear conditioning procedure we examined sex dependent expression of the immediate early gene c-Fos throughout the dorsal hippocampus, specifically within the CA1 (proximal - distal regions), CA3, and Dentate Gyrus, as well as the basolateral amygdala under varying placement-to-shock intervals (PSI) during both conditioning and memory retrieval. Consistent with most literature our behavioral results indicate sex dependent differences in context fear retrieval with increased context exposure. Males generally displayed greater context fear retrieval compared to females at increased context exposure times. Interestingly, we observed differences in c-Fos expression within the sub-regions of the hippocampus, particularly within the dentate gyrus and CA1 regions that are uniquely driven by context exposure time and the occurrence of a footshock. Our findings suggest that differences in the rate in which male and female mice form a representation of the context may be associated with differences in encoding- related activation of CA1and dentate gyrus neurons.

D'Andrea W *The Importance of Engagement: Understanding the Importance of Physiological Arousal in Reducing the Impact of Trauma*
The importance of engaging with emotion has been highlighted across

multiple theoretical traditions. However, the field has differed in its attention to up-regulation vs down-regulation of emotion. But the up-regulation of emotion may be necessary for multiple important functions in trauma recovery, such as connecting socially, consolidating learning, emotional expression and awareness, and experiencing pleasure. Indeed, when people are devoid of emotional expression, their accounts of trauma may be called into question, with consequences like denial of benefits, mistakenly assuming recovery from trauma, or disbelief in testimony. This talk will use evidence from psychophysiological research to examine the negative impact of emotional disengagement. Data will be drawn from laboratory and treatment studies.

de Solis CA, Holehonnur R, Kim LJ, Jones LE, Daison DK, Vuong DT, Khakoo SF, Ploski JE *Overexpression of GluN2A or GluN2B within neurons of the mouse basal and lateral amygdala alters amygdala dependent mnemonic processing*

NMDARs are heteromeric ionotropic glutamate receptors located on the postsynaptic neuronal membrane. These receptors are composed of an obligatory GluN1 subunit, and GluN2 subunits. Based on previous published literature, we hypothesized that differential expression of GluN2A and GluN2B subunits of the NMDA receptor within neurons of the amygdala might influence the acquisition, extinction and the induction of memory reconsolidation for an amygdala dependent fear memory. In order to examine this, we generated recombinant viral vectors designed to express these subunits before or after learning. Specifically, we generated lentiviruses designed to express GluN2A/B subunits from the TRE3G promoter that could be used in Îś-CaMKII-tTA mice to obtain neuronal specific expression of these subunits. To examine the how overexpression of these subunits influences fear acquisition and consolidation we bilaterally infused these viruses into the BLA of Îś-CaMKII-tTA mice and 14 days post infusion, we subjected them to auditory fear conditioning. Our results indicate that while short term memory (STM) remained unaltered in these animals, overexpression of GluN2A impaired long term memory

(LTM), while overexpression of GluN2B enhanced LTM. We are currently examining how overexpression of GluN2A and GluN2B within BLA neurons influences fear extinction and the induction of reconsolidation updating.

DeAngeli ND, Fournier DI, Todd TP, Bucci DJ *Disambiguating the contribution of parahippocampal regions to retrieval and extinction of recent and remote fear memories*
The postrhinal cortex (POR) is part a network of posterior cortical regions that provide the hippocampus with processed sensory information. Prior lesion studies have demonstrated that POR is critically involved in recent and remote contextual fear conditioning (Burwell, Bucci, Sanborn, & Jutras, 2004), but not in recent cue-specific fear memory (Bucci, Phillips & Burwell, 2000). It is unknown if the POR is critical for cue-specific retrieval of remote cued fear memories. Other cortical association areas, such as the retrosplenial cortex, have time dependent roles in retrieval of cued fear memories (Todd, Mehlman, Keene, DeAngeli, & Bucci, 2016), but no known roles in extinction and renewal of memories (Todd, Jiang, DeAngeli, & Bucci, 2017). Thus, we tested if the POR is necessary for the retrieval, extinction, and renewal of either recent or remote memories. Experiment 1 tested the impact of 1-day post training lesions on renewal of extinguished fear. Lesions made 1-day post training did not affect recall or extinction of conditioned fear. Additionally, lesions did not affect renewal, indicating that contextual encoding or retrieval of extinction does not depend upon the POR at recent time points. Experiment 2 tested the impact of lesions made 28-days post training. Like the recent time point, lesions did not impact recall or extinction of conditioned fear. However, lesions did impact renewal of a remotely conditioned tone fear memory suggesting a time dependent role of the POR in encoding or retrieval of extinction.

Delamater A *Learning about reward identity and time: A multi-componen approach*
Studies of Pavlovian conditioning have often assumed that associa-

tions between conditioned and unconditioned stimuli (CS-US) mediate the behavioral changes that underlies such learning. A considerable amount of work has attempted to characterize the informational content of those assumed associative structures that seem to participate in Pavlovian learning, and much progress has been made showing that distinct neural mechanisms mediate learning about a reward's identity (i.e., what it is) and its more general motivational value. I will present the results from both neurobiological and behavioral studies conducted in our lab that suggests a similar dissociation may exist between learning about a reward's identity and timing. These results suggest to us that learning "what" reward will occur and "when" it will occur may entail separable components of learning, and I will discuss the challenge this poses for further theory and research.

Della Valle RB, Chamness M, Moulton E, Knox D *Single prolonged stress enhances Akt signaling in the amygdala during fear memory formation*

Single prolonged stress (SPS) exposure results in extinction retention deficits in rodents and is often used to model post traumatic stress disorder in humans. Recent research we have conducted suggests SPS-enhancements in fear memory could contribute to extinction retention deficits in the SPS paradigm. Previous studies have found that SPS increases baseline levels of Akt in the hippocampus and Akt signaling modulates fear memory formation. These findings raise the possibility that SPS could enhance fear memory by enhancing Akt signaling in emotional circuits in the brain during fear memory formation. In turn, this enhancement in fear memory could lead to extinction retention deficits in the SPS model. In this study, we examined the effects of SPS on Akt phosphorylation at the ser473 site in the medial prefrontal cortex, amygdala, dorsal hippocampus, and ventral hippocampus at baseline and during fear conditioning. These brain regions were selected because of their roles in fear memory formation and/or regulation. SPS enhanced ser473 phosphorylated Akt (pAkt) in the amygdala during fear conditioning, but not at baseline. SPS had no other effects on pAkt or Akt levels in any other brain re-

gion. These findings demonstrate that SPS enhances Akt signaling in the amygdala during fear conditioning. Given that Akt signaling is critical for fear memory formation, these findings raise the possibility that extinction retention deficits in the SPS model is due, in part, to changes in fear memory strength driven by Akt signaling in the amygdala during fear conditioning.

Doan C, Vinnik M, Freestone DM *Mice weigh time intervals more than reward magnitudes*
Those with ADHD often have trouble waiting for delayed rewards, even if waiting leads to more reward. However, the underlying cause of this high discount rate is unclear; how do animals weight the importance of time intervals vs. reward magnitudes? Complicating this issue is the fact that those with ADHD also often show hyperactivity, which can mask impulsivity, even though they may come from different underlying mechanisms. In this study, we used the matching law task to independently manipulate both the intervals between rewards and the reward magnitudes over phases. Mice performed the task for two four-hour periods per day, once in the morning, and once approaching night. The VI schedule for each phase and choice options ranged from 1 to 30 minutes (exponentially distributed), and the magnitudes ranged from 1-5 pellets per reward. Unlike traditional discounting tasks, the matching law allows us to measure both hyperactivity and how mice weigh time intervals over magnitudes. Our results suggest that six of the seven mice were more sensitive to changes in the time intervals than in the reward magnitudes. Hyperactivity was not a predictor of either choice sensitivity or bias.

Dutta S, Gilman TL, Fouty J, Cecil C, Adkins S, Jasnow AM *Role of the nucleus accumbens in cued fear extinction*
The nucleus accumbens (NAcc), consisting of core and shell subregions, has primarily been studied as a locus mediating the effects of drug reward and addiction. This is due to the region's role of ascribing valence and salience to internal and external cues. In light of this central function, we sought to explore the influence of the NAcc on cued

fear expression and extinction. Specifically, we examined the role of glutamatergic receptors in mediating these fear-related processes. Using adult male C57BL/6 mice, we stereotaxically implanted bilateral cannulae directed at the NAcc. Twenty-four hours following fear training to an auditory tone, we infused the AMPA antagonist NBQX or the metabotropic glutamate receptor class I (mGluRI) antagonist AIDA into the NAcc 5 min prior to expression testing/extinction training. . Fear expression was significantly attenuated by NBQX infusion, whereas AIDA had no immediate influence on fear expression. However, when mice were tested 24 h later for extinction retention, those previously infused with AIDA exhibited enhanced fear, indicating AIDA had impaired the consolidation of fear extinction. These findings are the first to characterize a role of glutamatergic receptors in cued fear expression and extinction processing. Our data indicate ionotropic glutamatergic signaling in the NAcc is important for mediating behavioral fear expression. Conversely, metabotropic glutamatergic signaling appears critical for reassigning valence to a previously aversive cue (extinction). Current studies involve targeting the core and the shell separately to study how glutamate mediates fear processing in these sub-regions.

Eddy MC, HuszÃąr R, Bucci DJ *The retrosplenial cortex and its connections with the medial prefrontal cortex are crucial for inhibitory learning and behavior.*

The prefrontal cortex (PFC) has a well-established role in response inhibition and behavioral flexibility, both of which are often guided by information about the current environmental setting, or context. Contextual cues frequently indicate whether or not a particular response will result in a favorable outcome; if not, then that behavior should be inhibited. Research from our laboratory as well as others has established that posterior cortical regions, such as the retrosplenial cortex (RSC), are essential for encoding and retrieving contextual information. Yet, it remains largely unclear if and how the PFC and RSC interact to support the use of contextual information to guide behavior. In these experiments, we test the hypothesis that contextual information

projected to the medial PFC from RSC is essential for adaptive selection of behavior. In experiment 1, rats with electrolytic lesions of the RSC were tested on an extradimensional set-shift task. Set-shifting is a test of cognitive flexibility which requires rats to first learn a simple discrimination, and then to adapt to a rule "shift." During this shift, responding based on the previously learned rule must be inhibited in favor of the new rules that indicate reward availability. Lesions of the mPFC have been shown to selectively disrupt performance of the rule shift while leaving simple discrimination performance intact. We found that rats that had pre-training RSC lesions were impaired at the shift portion of this task, but performed similarly to sham rats during the initial discrimination, suggesting input from the RSC is necessary for optimal performance of the rule shift. In experiment 2, we targeted and selectively inhibited neurons projecting from RSC to mPFC during a test of operant extinction and renewal. Rats were trained to lever press in one context (context A) and then extinguished in a different context (B). Testing occurred in extinction (no reward available) in both contexts. Before testing began, neurons in the mPFC receiving projections from RSC were inhibited. Preliminary results from this experiment suggest that selective inhibition of this pathway results in increased responding (compared to controls) in both the acquisition (A) and extinction (B) contexts, indicating an inability to inhibit lever pressing. Taken together, these results suggest that projections from the RSC to mPFC are key for inhibitory control of behavior.

Ellis AS, Bongiovanni A, Bhakta S, Knouse M, Thomas A, Peer K, Wimmer ME *Paternal morphine exposure causes maladaptive behavior in male progeny*

Drug addiction is a crippling public health concern that inflicts massive burdens on our economy and society. The number of opioid-related drug overdose deaths has more than quadrupled in the past decade. The ripple effects of drug abuse extend far beyond the addicts to harshly impact families and social networks. Nevertheless, therapeutic options to treat addiction are limited. Recent studies in rodents indicate that children of fathers who consumed drugs around the time

of conception show altered brain function and behavioral abnormalities. Environmental insults, such as exposure to drugs of abuse, can affect the brain development of future generations via epigenetic reprogramming of the germline. Epigenetic inheritance refers to traits transmitted from parents to progeny via mechanisms independent of changes in the DNA sequence. According to recent reports, the fathers of 5 million children are afflicted by substance abuse, which underscores the need for further studies. To address this question, we have developed a multigenerational animal model of paternal opioid exposure. In our experiments, male rats self-administered morphine and were bred to drug naïve females to produce male and female offspring. We found that male, but not female progeny of morphine-exposed sires show increased morphine self-administration. This phenotype appeared to be reward specific, in that sucrose and cocaine self-administration were unaffected by paternal opioid exposure. These findings have laid the groundwork for identifying areas of vulnerability in the children of opioid-abusing fathers as well as biomarkers related to addiction susceptibility. NIDA K01 DA039308

Farley SJ, Albazboz H, Freeman JH *Modulating Acquisition of Delay Eyeblink Conditioning with Optogenetic Excitation and Inhibition of the Rat Amygdala Central Nucleus*

Pharmacological inactivation of the amygdala central nucleus (CeA) impairs delay eyeblink conditioning (dEBC), a well-known cerebellar dependent task (Farley 2016). In order to better understand amygdalar modulation of cerebellar learning, we used gain-of-function and loss-of-function optogenetic techniques in the CeA with adult rats training in dEBC. For gain-of-function, channelrhodopsin (AAV-hSyn-hChR2(H134R)-EYFP) transduced CeA cells which were later stimulated with 473nm (blue) light. Archaerhodopsin (AAV-hSyn-eArch3.0-EYFP) was used as the loss-of-function opsin stimulated by 561nm (green) light. Control animals received AAV-hSyn-EYFP to their CeA. After recovering from optical implant surgery, rats commenced training in five, 100-trial sessions of dEBC. Trials consisted of tone (CS) / shock (unconditioned stimulus [US]) pairings. Blue light was illumi-

nated at 20 Hz (5 ms pulses) for the ChR2 animals, and green light was constantly on for Arch animals. In all cases, laser stimulation was limited to the duration of the conditioned stimulus (CS) period only.

Animals trained with Arch stimulation showed impaired learning relative to controls, whereas, animals trained with ChR2 stimulation showed a slightly enhanced learning curve. The rate of conditioned responses for ChR2 animals was only slightly enhanced compared to controls. However, CR onset latency was significantly lower during acquisition with ChR2 stimulation compared to controls and Arch animals. CR amplitude and CR area were also significantly increased for the ChR2 animals.

Similar to our previous findings (Farley, 2016), no metrics pertaining to the unconditioned response (peak, latency, area, etc) revealed group differences or interactions across opsin groups. This suggests that amygdala modulation during cerebellar associative learning may not be occurring through the US pathway. Since all of the statistically significant findings were across CR characteristics, it may be that perturbations to CeA output effect the sensory input of the CS to the cerebellum. Thus, the CeA may have a gate-like role for sensory information in pre-cerebellar areas, e.g. the pontine nucleus. Future studies will utilize optetrode recordings in the CeA to verify excitation or inhibition manipulations as used above. National Institute of Neurological Disorders and Stroke grant NS088567

Fast CD, Ellis H, Webb EK, Lewon M, Brotheridge S, Cox C *Investigating peak shift in an olfactory discrimination: Lessons for animal scent detection*

For the past 20 years, APOPO, a Belgian non-profit humanitarian organization, has trained African giant pouched rats (Cricetomys ansorgei) to detect buried landmines in former conflict zones. Since 2007, APOPO has expanded operations in developing countries to combat tuberculosis, the world's deadliest infectious disease, by training pouched rats to detect Mycobacterium tuberculosis in human sputum samples. APOPO's Research & Development sector conducts

multi-faceted research to inform and optimize training procedures and scent detection applications. We investigated if pouched rats demonstrate peak shift after discrimination training with different concentrations of a single odorant. Some rats were reinforced for indication behaviors in response to high, but not low, concentrations of the odor (H+/L-), while other rats received training with the reverse contingencies (H-/L+). Generalization of the indication response was measured across a range of odor concentrations before and after discrimination training. The results have implications for olfactory learning mechanisms and could inform best training practices to optimize rat scent detection applications. This research was generously supported by the Firmenich Family

Ferrara NC, Cullen PK, Pullins SE, Helmstetter FJ *Thalamic inputs onto the amygdala regulate fear memory retrieval*
Pavlovian fear conditioning provides a way to investigate memory formation and retrieval. During fear conditioning, a conditional stimulus (CS) is paired with an aversive outcome and the CS acquires aversive value over several pairings. The CS may then be presented during a retrieval session where fear responding is measured as an indicator of memory strength. Retrieval sessions allow for the incorporation of new information into the original memory trace by destabilizing amygdala synapses, which is accompanied by changes in synaptic expression of AMPA receptors. Inhibition of protein synthesis-dependent plasticity in the amygdala immediately following a retrieval experience impairs long-term memory retention and disrupts AMPA receptor synaptic expression. Previous work shows that terminals of auditory thalamic (MgN) neurons onto cells in the lateral amygdala are immediately presynaptic to AMPA receptor subunits, suggesting that MgN input may play a role in amygdala-dependent memory through regulation of AMPA receptor dynamics. However, very little is known about the sensory inputs to the amygdala that regulate fear memory at retrieval. Local inhibition of the MgN activity using pharmacological agents prior to fear conditioning, but not prior to retrieval, can disrupt memory, but pathway specific optogenetic manipulation pro-

vides more precise tool that potentially allows for isolation of MgN-LA connections. Recent work has shown that optogenetic terminal stimulation of thalamic and cortical inputs onto the amygdala during conditioning can serve as a CS to simulate auditory fear conditioning when paired with a UCS and that this is dependent on glutamatergic synaptic transmission. Importantly, groups conditioned with optogenetic stimulation as a CS show that terminal stimulation closely resembles auditory fear memory retrieval, suggesting a role for thalamic and cortical terminals in the amygdala during fear memory reactivation. Here groups undergo auditory fear conditioning followed by a brief retrieval session to characterize the role of MgN terminals in the amygdala during recall. We found that silencing MgN terminal activity during CS presentations at retrieval impaired fear responding, suggesting that MgN inputs to the amygdala are necessary for the retrieval of an auditory fear memory. Other experiments address if MgN terminal silencing alters anisomycin-induced amnesia following memory retrieval and synaptic destabilization evidenced by changes in AMPA receptor trafficking in the amygdala. NIMH R01 MH069558

Fink AJP*, Schoonover CE*, Axel R *A naturalistic assay for measuring behavioral responses to aversive stimuli at millisecond timescale*

Many assays of Pavlovian conditioning rely upon measures of behavioral phenomena that play out over many seconds, such as salivation, licking, time spent freezing or avoidance of a conditioned stimulus. These quantities are difficult to relate to the neuronal events that govern them, which unfold on a timescale of milliseconds. We have designed a Virtual Burrow Assay (VBA) to measure the behavioral responses of head-fixed mice to aversive stimuli, which detects behavioral transitions at a temporal resolution that permits comparison with neuronal processing. The VBA simulates a scenario in which a mouse, poised at the threshold of its burrow, evaluates whether to remain exposed to potential threats outside or to retreat inside an enclosure. It consists of a light enclosure (virtual burrow) affixed to a frictionless rail that a head-fixed mouse can displace along its body's

anterior-posterior axis. When presented with aversive stimuli, mice exhibit a stereotyped retreat whose onset is determined by measuring the position of a moveable burrow. This withdrawal, which requires no training, is characterized by an abrupt transition that unfolds within milliseconds—a timescale similar to that of neuronal dynamics, permitting direct comparison between the two. The VBA is capable of measuring aversion to both conditioned and innately aversive cues, as well as novelty detection; we have exploited these features to obtain head-fixed behavioral readouts of aversive Pavlovian conditioning, sensory preconditioning, and unreinforced learning of sequences of neutral stimuli. The apparatus is compatible with standard electrophysiological and optical methods for measuring and perturbing neuronal activity.

Fisher H, Greig S, Weston A, Pickens CL *Three injections of anesthetic ketamine improve performance in a go/no-go reversal learning task and alter parvalbumin-positive neuronal expression in rats*
Previous research in our lab has found that three anesthetic doses of ketamine improve reversal learning in a go/no-go task in rats, but it is unclear whether all three doses are required to produce these alterations and how anesthetic ketamine exposure affects the neurobiological substrates of reversal learning. We examined whether 1, 2 or 3 anesthetic doses of ketamine would produce long-term changes in our go/no-go reversal learning task. We gave male Long Evans rats 0, 1, 2, or 3 (i.p.) injections of 100 mg/kg ketamine for three consecutive days. The rats were tested in a go/no-go reversal learning task beginning 19 days later. In the reversal learning task, rats were reinforced for pressing one lever (the "go" lever) and reinforced for withholding responding on another lever (the "no-go" lever). In order to pass the discrimination phase, the rats had to make 26 correct responses in a row for three consecutive days. Once the discrimination criterion was reached, the contingencies were reversed such that the go lever became the no-go lever and vice versa. To pass the reversal learning phase, the rats had to make 26 correct responses in a row for three consecutive days. No differences between

groups were observed in the discrimination phase. During reversal learning, the 3 injection group, but not the 1 or 2 injection groups, exhibited improved reversal learning compared to the saline group. To further characterize the neurobiological effects of anesthetic ketamine, we examined the density of parvalbumin- (PV) expressing GABA interneurons, which often exhibit changes following ketamine or PCP exposure. The 3 injection group exhibited decreased PV+ neurons in the prelimbic cortex, compared to the saline group. Additionally, the number of PV+ neurons in the dorsal medial striatum correlated with maintenance errors, errors made after the rat passed criterion (26 correct responses in a row) the first day but before they met criterion 3 days in a row, in the saline group. This correlation was not present in the 3 injection group. Maintenance errors in the 3 injection group correlated with PV+ neurons in the prelimbic and infralimbic cortex, but this correlation was not present in the saline group. This suggests 3 injections of anesthetic ketamine are needed to alter go/no-go reversal learning and our dosing regimen is likely changing neuronal processing and circuitry involved in our reversal learning task. Future research aims to identify which receptors are involved in anesthetic ketamine's long-terms effects on go/no-go reversal learning.

Fortune ES, Day NF, Coleman, MJ *When Brains Cooperate*
How do animals control cooperative behaviors, such as dancing a tango? To examine the behavioral rules and neurophysiological mechanisms by which animals coordinate their behavior during cooperative performances, we studied duet singing in plain-tailed wrens (Pheugopedius euophrys). Female and male wrens produce precisely coordinated duets that sound as if a single bird is singing. We are interested in how these birds use autogenous (self-generated) and heterogenous (other-generated) sensory feedback to coordinate patterns of spiking in CNS circuits for the control of duet performances. We captured birds, quantified the spectral and temporal features of their singing, and then implanted tetrodes into a telencephalic song control area 'HVC' of both birds. We observed robust premotor activity in

each bird during duets. Unexpectedly, despite the fact that behavioral experiments demonstrate that birds use acoustic cues to coordinate singing, we found no change in spiking in response to acoustic cues during duets or playbacks of songs. Subsequently, we anesthetized the birds with urethane and recorded the spiking responses of HVC neurons to playback of duet songs and other sounds. There was a strong correlation in the preference of neurons in female and male brains for different duet performances, suggesting a shared representation of the acoustic features of their duet songs. However, we found a dramatic sex difference in the timing of spiking activity between females and males. In females, neurons responded to both female and male syllables whereas in males, neurons responded primarily to female syllables. These differences in auditory responses are correlated with subtle differences in the role of each sex in the coordination of duets: females appear to have a greater role in the control of the timing and structure of duet performances. NSF IOS-0917918

Frankland PW *Optogenetic recovery of 'lost' infantile memories*
Neurogenesis persists throughout life in the hippocampus, and there is a lot of interest in how the continuous addition of new neurons impacts hippocampal memory function across development. Our studies in rodents have shown that high rates of neurogenesis during the post-natal period contribute to accelerated forgetting (i.e., infantile amnesia) (e.g., Akers et al [2014] Science). Our more recent studies address whether amnesia is associated with storage vs. retrieval failure. Using optogenetic approaches we find that otherwise 'lost' infant memories may be recovered via direct stimulation of ensembles of neurons that were active during initial encoding. Canadian Institutes for Health Research

Fraser KM, Janak PH *Feature-positive occasion setting is dependent upon neuronal activity in the basolateral amygdala*
Cues have myriad relationships with reward and we rely on features, such as contexts or discrete features, in the environment to disam-

biguate their predictive relationship to set the occasion for reward-seeking. As a result these contexts and features are referred to as occasion setters as they transform ambiguous reward-predictive cues into powerful incentive triggers. We have developed a model of occasion setting that is robust and amenable to investigations of its neurobiological underpinnings. We demonstrate that the feature-target relationship in this preparation is resistant to extinction and show that the conditioned reinforcing properties of the target cue is dependent on the presence of the feature. Additionally, we provide evidence that the basolateral amygdala is a critical locus for the expression of occasion setting as reversible inactivation of this structure produces a specific and selective impairment in linking feature-target pairings to produce proper reward-seeking. Together we provide evidence that occasion setters may act by regulating the incentive motivational value of reward-paired cues and that the basolateral amygdala is a candidate neurobiological structure for the regulation of occasion setting. NIH Grant R01 DA035943

Freestone DM, Donskoy B, Benson-Xu E, Sari D, Early K, Myers KP *Rats do not adjust their timing precision (but they can)*
Like other animals, a rat's time perception follows Weber's Law, their response variability scales linearly with the interval they time. The weber fraction () gives an upper bound on the animal's measurement error. Mice, rats, and humans can estimate their own measurement error to make optimal decisions, but it isn't clear whether they can adjust their measurement error in response to the task demands. In a series of studies, we used the switch task to impose different task demands on the rat, including (1) making the temporal discrimination harder, (2) extending the training, (3) increasing the overall reward, (4) giving asymmetric payoffs, (5) changing their diet, and (6) increasing hunger with ghrelin. We provide Bayesian estimates on the amount the weber fraction changed for each experiment, and show that the most probable result is that rats do not change their timing precision. The exception to this rule is that rats do systematically adjust their weber fraction when given asymmetric payoffs. We

conclude that rats largely do not adjust their timing precision, but they can. We discuss efficient coding as a possible explanation.

Gallagher, Michela *The Two-Way Street Linking Rodent and Primate Brains in Translational Research*
Great unmet needs exist in the treatment of brain disorders with little progress made over decades in which the field of neuroscience has flourished. This talk will be about bridging the gap between basic research using advanced tools in studies of the brain in laboratory animals and conditions in humans. In an emerging paradigm shift, the two-way street in translational research more closely ties our understanding of how the normal brain works with experimental approaches in therapeutic studies of brain dysfunction across species.

Gardner MP, Conroy JS, Styer CV, Schoenbaum G *Lateral orbitofrontal cortex inactivation dissociates devaluation-sensitive behavior and economic choice*
How do we choose between goods that have different subjective values, like apples and oranges? Neuroeconomics proposes that this is done by reducing complex goods to a single unitary value to allow comparison. This value is computed âĂŸon the fly' from the underlying model of the goods space, allowing decisions to meet current needs. Such behavior is termed âĂŸmodel-based' to distinguish it from pre-determined, habitual or âĂŸmodel-free' behavior. The lateral orbitofrontal cortex (OFC) supports model-based behavior in rats and primates, but it is less clear whether it is necessary for economic choice. Here we tested this question using halorhodopsin to optogenetically inactivate lateral OFC in rats (n = 9; control, n = 7) in a classic Pavlovian devaluation task and also during economic choice in rats. As expected, inactivation of OFC during the extinction test of the Pavlovian task following reinforcer devaluation disrupted behavior, yet surprisingly, behavior was unaffected by OFC inactivation on the economic choice task. NIDA IRP

Ghirlanda S, Enquist M *On the role of responses in Pavlovian con-*

ditioning
A defining feature of Pavlovian conditioning is that the unconditioned stimulus (US) occurs whether or not the animal performs a conditioned response (CR). This has lead quite naturally to the question: does learning, as well, occur whether or not a CR is performed? The issue was hotly debated between the 1930's and 1970's, by which time a consensus gradually emerged that CR acquisition is driven by CS-US pairings, and that CRs play a minimal role, if any. Here I revisit the question and develop new statistical techniques to evaluate whether CRs influence the course of learning. I present results suggesting that CRs play a decisive role in conditioning, at least in some experimental paradigms such as rabbit eyeblink conditioning and pigeon autoshaping.

Giustino TF, Fitzgerald PJ, Maren S *Locus coeruleus activation drives prelimbic cortical firing and induces relapse of extinguished fear*
Fear extinction is context dependent. That is, fear tends to relapse in settings outside the extinction context. Past work has demonstrated that the stress hormone norepinephrine (NE), produced by and released from the locus coeruleus (LC), is elevated in individuals with posttraumatic stress disorder (PTSD). How the LC-NE system contributes to fear relapse is largely unknown. Here, we used LC-specific DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) to examine how LC-NE contributes to both extinction retrieval (low fear) and fear renewal (high fear). Male rats received bilateral infusions of either AAV9-PRSx8-hM3Dq-HA (an excitatory DREADD) or AAV9-PRSx8-hM4Di-HA (inhibitory DREADD) into the LC. A subset of animals was also implanted with a 16 channel microelectrode array targeting the prelimbic (PL) and infralimbic (IL) subdivisions of medial prefrontal cortex. In animals expressing the excitatory DREADD, the ligand for these receptors (clozapine N-oxide; CNO) increased PL firing rates and markedly increased freezing to the extinguished CS in the extinction context (i.e., during retrieval). In contrast, while the inhibitory DREADD did not have strong effects

on freezing behavior, CNO dampened PL firing in these rats. These data suggest that LC-NE induces fear relapse by potentiating PL activity, which may be a new endophenotype for fear relapse that could be therapeutically targeted in individuals with PTSD.

Goode TD, Acca GM, Maren S *The bed nucleus of the stria terminalis mediates expression of fear to temporally unpredictable threats* The bed nucleus of the stria terminalis (BNST) is thought to control conditioned fear responses to contexts but not phasic cues. However, conditioned contexts may inevitably differ from discrete cues in terms of when the animal expects an aversive outcome to occur during presentation of the stimulus. The current experiments sought to examine whether temporal unpredictability of the aversive unconditioned stimulus (US) is a factor in the recruitment of the BNST. To test this hypothesis, we conditioned a single context with unsignaled footshock (2 sec, 1 mA) using either short (1 min; "temporally predictable") or long latencies (9 min; "temporally unpredictable") from the time the animal is placed in the context to when shock occurredâĂŤall rats were removed after 10 min total in the context. Following several separate training sessions, the BNST was reversibly inactivated using muscimol (a GABA receptor agonist) or NBQX (an AMPA receptor antagonist) just prior to a retrieval session in the conditioned context in the absence of shock. Results revealed that despite equal context exposure in the shock-associated context, inactivation of the BNST disrupted fear expression only to the context in which shock was temporally unpredictable. Next, we examined whether recruitment of the BNST to temporally unpredictable USs is dependent on the modality and duration of the conditioned stimulus (CS). We established a strong vs. weak predictor of footshock using forwards (i.e., CS-then-US; "temporally predictable") or backwards (i.e., US-then-CS; "temporally unpredictable") fear conditioning (CS = 10 sec, 2 kHz, 80 dB auditory cue; US = identical to above). Temporary lesions were hypothesized to disrupt fear expression solely to the backwards trained CS. Specifically, rats were fear conditioned using five or twelve training trials to either a forwards- or backwards-trained CS in context A.

A day later, rats were infused with NBQX and tested to the CS in the absence of the US. Similar to the results of the previous experiment, BNST inactivation attenuated fear to the backwards CS, but spared the forwards-trained CS. A follow-up experiment demonstrated elevated levels of the immediate early gene, c-fos, in the BNST following exposure to a backwards-trained CS, but not to a forwards-trained CS or in the absence of any CS. Collectively, these results suggest that fear evoked by temporally unpredictable CSs, whether contexts or cues or long- or short-duration stimuli, is mediated by the BNST. R01MH065961 to S.M.; McKnight Foundation Memory and Cognitive Disorders Award to S.M.; F31MH107113 to T.D.G.

Goodfellow MJ, Shin Y, Lindquist DH *Early developmental ethanol exposure increases IL-1 receptor signaling and diminishes long-term memory consolidation in male juvenile rats.*

Fetal alcohol spectrum disorders (FASD) are characterized by persistent impairments in higher-order cognition, including executive function, learning, and memory (Rangmar et al., 2015). Modeling FASD in rats, our lab administers ethanol (5 g/kg/day) over postnatal days (PD) 4 to 9, corresponding to the human third trimester. Postnatal ethanol induces acute and chronic neuroinflammation in the dorsal hippocampus, when assessed on PD10 (Drew et al., 2015) and PD28 (Tiwari and Chopra, 2011), respectively. The current study examines the persistent effects of early developmental ethanol exposure on neuroimmune activation and signaling in the hippocampus of ethanol-exposed (5E) juvenile (∼PD33) rats. Experimentally naïve subjects showed no significant treatment group differences in microglia or astrocyte cell counts or stain density. Cognitive function was assessed in separate juvenile rats using a hippocampal-dependent form of trace fear conditioning (TFC). At test, tone-evoked freezing was significantly diminished in male (but not female) 5E rats, relative to controls. Gene (Cd11b, Gfap, Il1b, and Tnf) and protein (IL-1Îš) expression was also measured in the hippocampus of homecage (baseline) controls and rats sacrificed 2 and 24 h following TFC. Il1b mRNA and IL-1Îš protein was significantly elevated in male (but not fe-

male) rats 24 h post-TFC. IL-1Îš release is tightly regulated, playing a key role in the maintenance of synaptic plasticity and long-term memory consolidation (Lynch, 2015). To determine whether enhanced IL-1Îš release and IL-1 receptor activation contributes to impaired TFC in 5E rats, an IL-1 receptor antagonist (Kineret) was injected into the cisterna magna 30 min prior to TFC. Relative to vehicle-injected rats, Kineret produced a significant increase in tone-evoked freezing in male 5E rats, whereas the drug had no significant effect in female 5E rats. Collectively, results suggest increased IL-1 signaling interferes with learning-dependent synaptic plasticity following TFC, hindering or limiting consolidation of the tone-shock associative memory in male 5E rats.

Gould TJ, Kutlu MG, Parikh V *Paternal Nicotine Exposure Alters Generational Fear Conditioning and Hippocampal Cholinergic Function*

Tobacco use remains to be the leading cause of preventable death in the US leading to various negative health consequences such as cardiovascular diseases and cancer. In addition to these health problems, a relationship has been established between smoking and psychological problems such as anxiety and stress disorders. Moreover, recently, studies have shown that the effects of nicotine use may be transgenerationally transmitted through epigenetic modifications. In the present study, we examined the effects of paternal nicotine exposure on fear learning in subsequent generations in order to understand the potential transgenerational influence of nicotine exposure on fear-related symptoms in anxiety and stress disorders. Specifically, male adult C57BL6/J mice received either chronic nicotine (28 days, 12.6 mg/kg/d) or chronic saline exposure. Then, the male and female offspring of nicotine (Nic-Sired) and saline (Sal-Sired) exposed mice were tested in contextual and cued fear conditioning. Our results demonstrated that paternal nicotine exposure resulted in enhanced cued and contextual fear learning in the subsequent generations (F1 and F2) compared to Sal-Sired mice and this effect was reversed when F1 generation, but not F2 generation, mice

received acute nicotine injections. Furthermore, Nic-Sired mice also showed more pronounced spontaneous recovery of fear when retested following extinction. We also found that although paternal nicotine exposure enhanced fear learning, non-emotional learning was not affected in Nic-Sired mice as they exhibited normal memory function in the Novel Object Recognition paradigm. Paternal nicotine exposure also did not alter performance in in the elevated plus maze and open field tasks excluding the possible confounding effects of anxiety and locomotor activity. Finally, we examined the general cholinergic activity in the Nic-Sired mice using nicotinic acetylcholine receptor (nAChR) binding and potassium and nicotine-evoked acetylcholine release in the dorsal and ventral hippocampus. Our results showed reduced ventral, but not dorsal, hippocampal cholinergic function in the Nic-Sired mice as well as increased nAChR binding in the whole hippocampus. In parallel, we also found increased DNA methylation in the ventral hippocampi of the Nic-Sired mice whereas this effects was absent in the dorsal hippocampus. Together, our results suggest that paternal nicotine exposure may result in alterations in the epigenome, which, in turn, leads to exaggerated fear learning and abnormal cholinergic function in subsequent generations. Grant Support: National Institute of Health (T.J.G., DA017949; V.P., DA037421)

Gunaydin LA (UCSF) *Afferent control of striatal circuitry in social and anxiety-like behaviors*

Anxiety disorders are some of the most common mental illnesses. Existing pharmacological therapies do not help a substantial fraction of patients, however these disorders respond particularly well to cognitive therapy. The prefrontal cortex has long been implicated in cognitive control and anxiety-related behaviors, although the precise downstream circuits and cell types mediating prefrontal control of anxiety are poorly understood. Here we use a combination of in vivo and in vitro optogenetic and electrophysiological methods to identify causal top-down prefrontal projections and postsynaptic targets that control anxiety-like behavior in mice. We found that optogenetic stimulation of medial prefrontal cortex (mPFC) projections to the dorso-

medial striatum (DMS) had an anxiolytic effect in the elevated plus maze. mPFC projection stimulation preferentially recruited striatal medium spiny neurons (MSNs) expressing the D1 type dopamine receptor. Directly stimulating these postsynaptic D1 MSNs was sufficient to recapitulate the anxiolytic effect of mPFC-to- DMS projection stimulation. Moreover, stimulating this fronto-striatal pathway was sufficient to rescue pathological behavior in a genetic mouse model of increased anxiety-like behavior. These results implicate a previously unexplored top-down pathway for anxiety control, and highlight a role for the DMS in modulating affective behavior in addition to its well-characterized role in motor and cognitive behaviors.

Gutierrez AG, Sunsay C *Pavlovian conditioning of social exploration to a transient cue*
Social conditioned place preference (SCPP) studies showed that the reward value of social interaction is amenable to the laws of associative learning such that it becomes associated with the physical properties of the context. However, social interaction involves varieties of motivations such as exploration of a novel conspecific, aggression, mutual grooming and mating-like actions. In order to study whether social exploration of a conspecific per se is rewarding, we used a conventional Pavlovian conditioning procedure in which access to a restrained same-sex rat served as a reward. Three dependent variables in three experiments showed that the reward value of social exploration becomes conditioned to a transient cue and it is also subject to extinction and spontaneous recovery. The results may help to elucidate the mixed results that were obtained with SCPP procedures.

Handy, JD, Avcu, P, Ko, N, Ortiz, A, Doria, MJ, Servatius, RJ *Facilitated Eyeblink Conditioning and Delayed Extinction in Active Duty Military Expressing Posttraumatic Stress Disorder Symptoms*
OBJECTIVE: According to a learning diathesis model of PTSD, perseverative fear and avoidance following trauma reflect inherent learning biases. Enhanced associative learning during eyeblink classical conditioning was previously reported in combat veterans expressing

PTSD symptoms, as well as those with behaviorally inhibited (BI) temperament, a vulnerability factor for PTSD. The present study extends this work in an active duty military sample. METHOD: United States Coast Guard personnel (N = 83) recruited from small boat stations were assessed for current PTSD symptoms and BI, after which they completed one session of eyeblink conditioning using a 50% partial reinforcement schedule. In partial reinforcement, paired trials (500-ms pure tone conditioned stimulus [CS] co-terminated with a 100-ms air puff unconditional stimulus [US]) were interpolated with 50% CS-alone trials. RESULTS: Consistent with previous work, there was a high degree of concordance between personnel classified as BI and those meeting criteria for PTSD. PTSD was associated with facilitated acquisition of the conditioned eyeblink response, as well as delayed extinction of conditioned responses. CONCLUSIONS: These results reinforce the relationship between BI and PTSD in an active duty military sample, extending previous observations in veterans and civilians. Further, the conditioning data are consistent with predictions derived from a learning diathesis model of stress and anxiety. Facilitated associative learning may thus represent an additional vulnerability for the development and maintenance of stress-related pathology. This research was supported by the Stress and Motivated Behavior Institute

Heroux NA, Robinson-Drummer PA, Rosen JB, Stanton ME *Neonatal ethanol exposure impairs the context preexposure facilitation effect (CPFE) in adolescent rats: Acquisition, retention, and reinforcement effects*

The context preexposure facilitation effect (CPFE) is a variant of contextual fear conditioning in which learning about the context, acquiring a context-shock association, and retention of contextual fear is temporally dissociated across three separate days. The CPFE requires both the medial prefrontal cortex and dorsal hippocampus during all three phases (Heroux, Robinson-Drummer, Sanders, Rosen, & Stanton, 2017; Robinson-Drummer, Dokovna, Heroux, & Stanton, 2016). Our lab has shown that the CPFE is particularly sensitive to neurobe-

havioral disruption caused by neonatal ethanol exposure during the third trimester equivalent of human pregnancy (i.e., PD7-9 or PD4-9 in the rat; Jablonski & Stanton, 2014; Murawski, Klintsova, & Stanton, 2012; Murawski & Stanton, 2011; Murawski & Stanton, 2010). Indeed, in both ethanol exposure scenarios (PD7-9 or PD4-9), 24-hr retention of the CPFE is abolished. Interestingly, our lab has recently shown that PD7-9 ethanol exposures leaves post-shock freezing intact, thus, suggesting spared context- and context-shock learning but impaired retention of the context-shock association (Jablonski & Stanton, 2014). The purpose of the current study was to extend these findings to the PD4-9 exposure window while also examining the effects of different levels of shock reinforcement on this impairment. From PD4-9, Long-Evans rats received oral intubation of ethanol (5.25g/kg/day, split into two daily doses) or underwent control sham-intubation (SI). On PD31, rats in both conditions underwent the full CPFE procedure consisting of context exposure (PD31), immediate-shock training with 1 or 2 shocks followed by a 3min post-shock freezing test (PD32), and a 5min retention test 24 hours later (PD33). Consistent with our previous reports, PD4-9 ethanol exposure abolished 24-hr retention of the CPFE in both 1-shock and 2-shock conditions. Interestingly, unlike our previous findings with PD7-9 exposure, post-shock freezing was partially disrupted in the 2-shock condition and abolished in the 1-shock condition. These results suggest that while impaired retention of the context-shock association is common to both PD7-9 and PD4-9 exposure windows, PD4-9 ethanol exposure impairs configural learning or consolidation on the preexposure day of the CPFE to a greater extent than PD7-9 exposure. These findings are of particular interest because of prior research highlighting impaired prefrontal neuroanatomy and function in the PD4-9 exposure scenario. Future studies will examine the neural correlates of this effect during context learning on the preexposure day of the CPFE, with particular emphasis on prefrontal cortex involvement in the ethanol-induced impairments. [NIH grant R01 HD075066-01A1 to MES and JBR]

Johnson AW *The influence of CS-US interval and US density on the expression of cue-potentiated feeding*
In the current studies, conditioned stimulus (CS) âĂŞ unconditioned stimulus (US) interval, and US density were manipulated to examine whether different behavioral forms of cue-potentiated feeding would be evoked. In Experiment 1, mice were trained to receive presentations of an auditory CS for 20 s during which a sucrose US was delivered at a density of 1/9 s (Group-20-s). A second group of mice received an auditory CS for 120 s and a US density of 1/49 s (Group-120-s). During training, a shorter CS duration and higher rate of US delivery resulted in greater acquisition of food cup responding, and during the test stage Group-20-s mice also displayed higher CS evoked lick rates, though all mice showed cue-potentiated feeding. An analysis of licking microstructure also revealed that Group-120-s mice displayed CS evoked licking behavior that reflected an increase in the perceived palatability of the sucrose US. In Experiment 2, mice were trained with a CS-US interval of either 9 s or 49 s. During training, there was an inverse relationship between CS-US interval and food cup responding, whereas during the test, only mice trained with the 49 s CS-US interval displayed cue-potentiated feeding. These findings are discussed with respect to the influence of US density and CS-US interval on associatively activated sensory and affective representations of a US, and contrast mediated effects resulting from presentation of excitatory and inhibitory conditioned stimuli.
R01DK111475

Kalmbach AS, Simpson EH, Balsam PD *Reward availability in the presence and absence of conditioned inhibitory cues is encoded by dopamine in the ventral striatum*
Conditioned inhibition of behavior occurs when a cue signals that an otherwise expected unconditioned stimulus will not occur. Based on the idea that temporal information regulates learning we hypothesized that differences in the delays to the next expected US in the presence and absence of a CS- will drive inhibitory learning such that the longer the CS-, the greater the inhibition. Furthermore, if the rate of

reward during the absence of the CS increases, the conditioned inhibition will be strengthened. Contingency theory predicts equivalent inhibitory learning regardless of the CS duration. We trained mice to press a bar to earn rewards on a random interval schedule. A tone (CS-) was then introduced during which time rewards (US) could not be earned. To test the first hypothesis, we varied the duration of the CS- from 20 to 80 seconds and found that inhibition of the bar press was faster and deeper as the CS- increased in duration. To test the second hypothesis, we varied the reward rates in the ITI and found that the higher the reward rate during the ITI, the greater and faster the conditioned inhibition. Finally, to see whether behavioral inhibition was encoded in dopamine (DA) signaling in the ventral striatum we measured DA transients using in vivo fast scan cyclic voltammetry in behaving mice. We observed a slow decrease in extracellular DA levels at CS- presentation and the DA level stayed low until cessation of the CS- when extracellular DA levels quickly return to baseline levels. Interestingly, the time course of the behavioral response differed from that of DA release in that the response rate decreased at CS- start and slowly ramped up during CS-. Together, these data support a temporal theory of conditioned inhibitory learning over a contingency theory. Furthermore, we discovered that learning about the CS- is encoded in dopamine signaling in the ventral striatum with slightly different temporal dynamics than the behavioral response. Our findings could provide better understanding of the mechanisms underlying inhibitory control of behavior as well as the mechanisms underlying deficits in inhibiting action observed in some psychiatric conditions, including ADHD and schizophrenia.

Kaminer J, Diaz-Acevedo MA, Espinoza DG, Tepper JM, Koós T, Shiflett MW *Effects of Striatal TH-Interneuron Lesions on Goal-Directed Instrumental Behavior*

Identifying the specific contribution of the neostriatum during learning represents one of the central problems in the study of the basal ganglia. The classical investigation of the best understood learning systems in the brain has been greatly facilitated by the possibility of

gaining insights into computational and cellular mechanisms from detailed understanding of the anatomical and physiological organization of key brain areas. In contrast, the understanding of the functioning of the neostriatal circuitry remains too rudimentary to provide analogous insights. Here we investigated the behavioral effects of lesioning a class of genetically defined striatal interneurons (tyrosine-hydroxylase interneurons, THINs) in transgenic mice. The loss of this cell population was not associated with detectable impairments in movement or motor learning, suggesting that the deficits were not due to gross disruption of striatal dynamics. Lesioned mice also exhibited normal levels of anxiety and motivation. Importantly however, mice with restricted THIN lesions to the dorsomedial neostriatum were dramatically impaired in the learning and/or recall of action-outcome associations. Specifically, THIN-lesioned mice showed no devaluation effect on instrumental responding following selective satiety of the instrumental outcome. ÂăSimilarly, THIN-lesioned mice showed no invigoration of instrumental responding by outcome presentation in an outcome reinstatement test. We suggest that the detailed understanding of the circuitry of these interneurons, the ability to investigate their activity in behaving mice and the defined functional impairment associated with their deletion may provide an important new paradigm for studying the specific striatal mechanisms of instrumental learning in rodents. Supported by US National Institutes of Health grant R01 NS072950 to T.K. and J.M.T., NIH-Minority Biomedical Research Support Training Grant 1R25GM096161-06 to M.D. at Rutgers University-Newark, and Rutgers University IMRT-NTT.

Kass MD, McGann JP *Persistent, generalized hypersensitivity of olfactory bulb interneurons after olfactory fear generalization*
Generalization of learned fear from previously threatening stimuli to novel but related stimuli can be beneficial, but if fear overgeneralizes to inappropriate situations it can produce maladaptive behaviors and contribute to pathological anxiety. Fear generalization is believed to involve interactions between cortical sensory regions and higher-order structures such as the amygdala and prefrontal cortex. How-

ever, the contributions of low-level sensory pathways to fear generalization are poorly understood. Here, we explored the neurosensory consequences of fear generalization in a mouse model of olfactory fear learning. We performed in vivo optical neurophysiology to visualize odor-evoked neural activity in populations of periglomerular interneurons in the olfactory bulb before and after individual mice underwent an odor-cued fear conditioning paradigm designed to produce generalized fear of odors. Specifically, conditioning consisted of one day of training with 10 trials of a $\sim$15 sec odor (the CS) that was paired with a strong footshock. Behavioral and neurophysiological changes were assessed in response to a panel of odors that varied in similarity to the threat-predictive odor one day and one month after fear conditioning. Mice that underwent fear conditioning exhibited equals levels of freezing behavior in response to the CS and to other non-threatening odors one day after training, and this generalized fear response persisted for up to at least one month after learning, whereas control subjects exhibited little freezing in response to the same odor panel during either the 1-day or 1-month behavioral tests. Freezing behavior was significantly correlated with large changes in odor-evoked periglomerular cell activity, including a robust, generalized facilitation of the response to all odors, broadened odor tuning, and increased neural responses to lower odor concentrations. This generalized sensory plasticity occurred within 24 hours of conditioning, persisted for at least one month, and was detectable even in the first moments of the brain's response to odors. The finding that generalized fear includes altered early sensory processing of not only the threat-predictive stimulus but also novel though categorically-similar stimuli may have important implications for learning-dependent plasticity in downstream coding regions as well as the etiology and treatment of anxiety disorders with sensory sequelae. This work was supported by The National Institute on Deafness and Other Communication Disorders [R00 DC009442 and R01 DC013090 to JPM and F31 DC013719 to MDK] and The National Institute of Mental Health [R01 MH101293 to JPM].

Kastner S *Neural network dynamics for attentional selection*
Natural scenes are cluttered and contain many objects that cannot all be processed simultaneously due to capacity limitations of the visual system. Selective attention refers to a set of mechanisms that route behaviorally relevant information through large-scale cortical networks. I will discuss studies performed in two primate brain models, the human and the macaque monkey, using a variety of different techniques including fMRI, ECoG and single-cell physiology. First, I will discuss how large-scale networks mediating perception and cognition can be identified using functional brain imaging. Second, I will discuss physiology studies revealing temporal dynamics in a distributed large-scale network that mediates the selection of behaviorally relevant information. Particularly, while there is evidence that populations of cortical neurons synchronize their activity to preferentially transmit information about attentional priorities, it is unclear how cortical synchrony across a network is accomplished. I will discuss the unique role of thalamo-cortical interactions in influencing cortical networks to optimize their communication. These studies are complemented by ECoG recordings from human epilepsy patients using identical behavioral paradigms providing a mechanistic understanding of the coding principles that best predict behavior in both primate species.

Keiflin R, Pribut HJ, Shah NB, Janak PH *Dissociable Roles of Ventral Tegmental and Substantia Nigra Dopamine Neurons in Reinforcement Learning*
Dopamine (DA) neurons in the ventral tegmental area (VTA) signal reward prediction errors (RPEs) and their activation constitutes a teaching signal that promotes learning about the events leading up to reward. DA neurons in the Substantia Nigra (SNc) also encode RPEs but their functional role in error-correction learning is unclear. Moreover the learning strategy engaged by RPEs remains largely unknown. RPEs could promote pure value learning, independently of the representation of the outcome (=model-free). Alternatively, RPEs could contribute to the construction of internal models of the task, allow-

ing predictive cues to signal the specific identity of their paired outcome (=model-based). Therefore, the purpose of this study was to determine the functional role(s) of the phasic activity of VTA- and SN-DA neurons in reinforcement learning. We used optogenetic tools in TH-Cre transgenic rats to selectively activate VTA- or SNc-DA neurons in several Pavlovian or Instrumental conditioning preparations, designed to probe the content of learning. We found that: 1) In a Pavlovian "blocking" paradigm, the activation of VTA-DA neurons during expected sucrose consumption mimics RPE and restores (unblocks) learning about a redundant and normally ignored target cue. In contrast, activation of SNc-DA neurons does not promote Pavlovian learning (learning remains blocked). 2) The expression of VTA-DA dependent learning is virtually abolished following sucrose devaluation (by lithium-induced taste aversion), which indicates that the learned association integrates a representation of the sucrose outcome (=model-based learning). 3) Activation of VTA- or SNc-DA neurons serves as potent reinforcer of intracranial self-stimulation behavior. However, the reinforcing effect of SNc-DA neurons activation is limited to immediate prior actions, while the activation of VTA-DA neurons sustains the acquisition of a long chain of responses. Together, these findings reveal that the activation of VTA- or SNc-DA neurons engages largely dissociable learning processes. Contrary to the dominant view that reduces DA-RPEs to pure value learning (=model-free), we found that VTA-DA neurons are capable of participating in complex model-based predictive learning. In contrast, the role of SNc-DA neurons appears limited to stimulus-response mapping. These results are reminiscent of the actor-critic reinforcement algorithm, based on the notion of a separation of labor between a reward-prediction module and an action-selection module, but do however call for revision of this model to incorporate model-based processes. NIH Grant DA035943

Keiser AA, Pan PL, Tronson NC *Sex-specific decrease of remote context fear memory*

Disorders of fear and anxiety including post-traumatic stress disorder

(PTSD) are more prevalent in women than in men. Recent work from our laboratory and others has demonstrated sex differences in fear-related memories that may contribute to this greater susceptibility in women. Given the long-lasting nature of context fear memory, and the role of circuit dynamics during systems consolidation, we examined sex differences in retrieval of remote context fear memory. Unlike males, females showed reduced retrieval of context fear eight weeks after fear conditioning, compared with retrieval of a recent memory. Interestingly, this impairment in retrieval was only observed with background fear conditioning (in which a tone is paired with shock), but not foreground context fear conditioning (in which context is the sole CS). Previous work has established that, in males, the hippocampus is necessary for background, but not foreground context fear conditioning. Thus, our current data suggest sex differences in recruitment of the context fear memory circuit results in less robust remote context memory in females after background context fear conditioning. To examine the activation of this neural circuit after remote memory retrieval in females compared with males, we used cfos immunohistochemistry. Females showed higher levels of cfos activation in ventral hippocampus, basal amygdala, and retrosplenial cortex after retrieval of background context fear memory compared with males. This pattern of activation is unlikely to explain sex differences in remote context memory retrieval, however, as this pattern was also observed after foreground context retrieval. Furthermore, we observed greater cfos activation in dorsal hippocampus during retrieval of foreground compared with background context fear conditioning in both sexes. It remains unclear whether the observed cfos activity is due to retrieval of context memory, or due to other context-exposure related memory processing. Here we demonstrate decreased remote context memory in females, only in background fear conditioning, and sex specific patterns of cfos activity regardless of training protocol. Together with our previous work demonstrating sex differences in activation of hippocampus and amygdala during recent context fear memory retrieval, the present findings suggest that males and females may recruit differential circuits during systems consolidation and during retrieval of

remote memories. NDSEG Fellowship to AAK

Kenney L, Nussbaum H, Gotthard GH *Reminder Treatment Effective for Reversal of Cycloheximide-Induced Amnesia in Rats*
Reconsolidation theory suggests that amnesic agents produce permanent memory disruption, while retrieval failure theory suggests that "lost" memory can be recovered following reminder treatments. The current study examined these theories by training rats to discriminate between cups of scented sand for buried cereal rewards. One day following training, memories were reactivated via a single extinction trial, followed by intraperitoneal administration of cycloheximide (CHX; 1 mg/kg) or vehicle (VEH; 1 mg/kg saline). One week later, rats received a non-reinforced test trial during which latency to dig was recorded. Some rats then received a two-minute reminder (CHX/REM: n=10 and VEH/REM: n=9), which consisted of three cereal rewards presented in a novel context. Non-reminded rats (CHX/NoRE n=11) were placed into the same novel context for two minutes without receiving the food reminder. All rats then received a second nonreinforced test trial. Latencies during Test 1 were significantly longer for CHX than VEH rats [t(28) = 2.30, p = .029; partial η^2 = .185], which indicated that cycloheximide induced amnesia for the discrimination task. Differences in latencies on Test 2, after the reminder treatment, were marginally significant [F(2, 27) = 3.08, p = .062; partial η^2 = .186], with a trend toward shorter latencies in CHX/REM than CHX/NoREM. When examining latency for CHX/REM rats that dug after the reminder (i.e., 6 out of 10 rats), a paired samples t-test revealed a significant difference in latency from Test 1 to Test 2 [t(5) = 4.33, p =.008]. These results support a retrieval failure perspective because amnesia was reversed (in 6 of 10 rats) with a noncontingent food reminder.

Kirry AJ, Herbst MR, Twining RC, Gilmartin MR *Direct communication between the medial prefrontal cortex and the basolateral amygdala in the formation of a trace fear memory.*
The association of a neutral conditional stimulus (CS) and 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. A subset of PL cells exhibit sustained firing in response to a CS that persists until UCS delivery, and this trace interval activity is required for memory formation (Gilmartin & McEchron, 2005; Gilmartin et al., 2013). While this suggests that the PL may provide a bridging signal to link the CS and UCS in memory, it is unclear how and when the PL must communicate with the amygdala for learning to occur. Here we selectively manipulated PL inputs to the amygdala using projection-targeting optogenetics and intersectional viral-mediated chemogenetics during training. The PL-BLA connection was silenced during the trace interval by delivering laser light to PL ArchT-expressing terminals in the BLA on each of six training trials. ArchT and GFP controls (n = 5/group) were tested for memory retention the following day in the absence of laser stimulation. In a separate study, we activated this PL-BLA pathway during training by stimulating PL ChR2-expressing terminals in the BLA (n = 8/group). Neither optogenetic manipulation affected the formation of a trace fear memory, but stimulating this pathway enhanced the expression of a previously acquired fear memory. These results suggest that direct input to the BLA from the PL during the trace interval is not required for learning. We next used an intersectional chemogenetic approach to silence this pathway during conditioning and test the need for PL to BLA communication more generally in the formation of a trace fear memory. We delivered a retrograde virus containing CRE recombinase in the BLA and a virus containing the CRE-dependent inhibitory DREADD to the PL. Clozapine-n-oxide was given prior to training (1mg/kg and 5 mg/kg) to inactivate direct PL to BLA communication. Initial results support the conclusions from the optogenetic experiments that direct PL-BLA communication is not needed for trace conditioning. This suggests that the BLA does not directly integrate a prefrontal bridging signal to drive CS-related plasticity in the amygdala. In parallel, we are testing the importance of BLA in-

put to the PL in memory formation, which together with our PL-BLA experiments will determine whether communication between the PL and BLA is needed for the formation of a trace fear memory. Whitehall Foundation Research Grant 2014-08-67. National Science Foundation IOS:1558121

Latsko MS, Jasnow AJ *Corticosterone ameliorates the adult social behavior deficits caused by periadolescent social defeat*
Adolescent social stress can severely impact appropriate adult social behavior and stress responsiveness and may lead to greater risk of stress-related disorders later in life. Our lab utilizes a mouse model in which periadolescent (P30) male mice are subjected to repeated aggressive social encounters, followed by tests for social interaction 24 hours (P32) and 30 days (P62) after the last social defeat. When periadolescent mice are tested 24 hours after social defeat, defeated mice interact similar to non-defeated controls, suggesting a negligible immediate effect of social defeat. However, when the same mice are tested again in adulthood, some display social avoidance, whereas others display normal social interaction comparable to non-defeated controls. Our lab has previously identified that increased endogenous glucocorticoid (corticosterone) secretion is correlated with normal social behavior in adulthood following periadolescent social defeat. The current set of experiments aim to test if corticosterone plays a causative role in shaping adult social behavior after periadolescent social defeat. Corticosterone administered after periadolescent social defeat in drinking water overnight promoted normal adult social behavior, ameliorating the deficits caused by social defeat. This effect was replicated with an intraperitoneal injection of corticosterone at the start of the dark phase of the light:dark cycle. We further identified that central glucocorticoid receptors (GR) likely mediate this effect. Administration of low dose dexamethasone did not improve adult social behavior following periadolescent social defeat. In addition, pharmacological administration of a GR antagonist (Mifepristone) attenuated the enhanced social behavior produced by corticosterone administration. Together, these data demonstrate novel and endur-

ing positive effects of corticosterone administration on adult social behavior following periadolescent social defeat. Translationally, glucocorticoid administration has been used to alleviate the effects of trauma in humans. Our data suggest that glucocorticoids could provide long-term benefits in the face of adolescent trauma.

Lay BPP, Nicolossi M, Usypchuk A, Esber G, Iordanova MD *Infralimbic cortex regulation of overexpectation and extinction*
The ability to reduce outcome expectancies in the face of changing environmental contingencies is critical for survival so that effortful action is not engaged in search of unavailable rewards. Extinction and overexpectation are two paradigms that provide conditions under which outcome expectancies are reduced. In extinction, outcome expectation is reduced by omitting the delivery of an expected outcome. In overexpectation, similar reduction in outcome expectation is achieved by generating an expectation of double the outcome and delivering a single outcome (overexpectation). Both paradigms generate a negative prediction error, which drives a reduction in outcome expectancy. The infralimbic cortex (IL) has been implicated in regulating behaviour in line with extinction training in fear and reward albeit somewhat inconsistently. One view aimed at explaining these results along with the IL role in habitual responding is to suppose that the IL plays an important role in regulating stimulus-response, in contrast to stimulus-outcome, associations. Indeed, it is stimulus-response and not associations between the stimulus and sensory properties of the outcome that are altered during extinction training (Delamater, 1996; Rescorla, 1996). We used overexpectation in order to examine the role of the IL cortex in learning to reduce outcome expectancies in the presence of the outcome, thus reducing the possible influence of stimulus-(no)response associations. Our results show that IL inactivation during overexpectation learning has no effect on reducing outcome expectations, as seen by reduced responding on test. Inactivation of the IL in the same rats resulted in faster reduction in responding during a subsequent extinction learning phase, which did not translate into differences compared to controls on a subsequent

test of extinction retention. These results provide evidence that the IL regulates stimulus control over responding and not stimulus control over outcome expectations. FRQNT, BBRF, CRC Tier 2

LeCocq MR, Lahlou S, Chahine M, Padillo LN, Chaudhri N *Reinstatement and spontaneous recovery of Pavlovian-conditioned alcohol-seeking behaviour in rats*

Objective. The return of conditioned responding after extinction can be triggered by unsignaled exposure to an unconditioned stimulus (reinstatement) or by the passage of time (spontaneous recovery). However, these established effects have not yet been demonstrated in a Pavlovian conditioning procedure in which alcohol is the unconditioned stimulus (US). Methods. Male, Long-Evans rats (Envigo, 220-240 g on arrival) received 15 sessions of intermittent access to alcohol (15% ethanol; v/v) and water (Monday, Wednesday, Friday; 24 h sessions) in the home cage to induce high levels of alcohol consumption. Subsequently, rats received 12 Pavlovian conditioning sessions, in which a 20 s auditory conditioned stimulus (CS; continuous white-noise) was paired with 0.3 mL of alcohol that was delivered to a fluid port for oral consumption (8 CS trials/session; CS delivered on VT 280 s schedule; 2.4 mL EtOH/session). We report here that this schedule of alcohol delivery results in detectable levels of alcohol in the blood. Eight extinction sessions followed, in which the CS was presented without alcohol. In Experiment 1, separate groups of rats then received unsignaled alcohol or water (control) in the fluid port, as during Pavlovian conditioning but without the CS. A test session was conducted 24 h later, in which the CS was presented alone. In Experiment 2, the same rats received 8 additional Pavlovian conditioning sessions, followed by 8 extinction sessions, and then a test in which the CS was presented alone. In separate groups of rats, a 23-day delay was introduced either between Pavlovian conditioning and extinction, or between extinction and test. Results. In Experiment 1, CS-elicited port entries at test were significantly reinstated by prior, unsignaled exposure to either alcohol or water. In Experiment 2, a 23-day delay between extinction and test resulted in robust

spontaneous recovery of CS-elicited port entries, relative to rats that received the same delay between Pavlovian conditioning and extinction. Reinstatement and spontaneous recovery effects were characterized by an increase in the number and duration of CS-elicited port entries, as well as a reduction in latency to initiate the first CS-elicited port entry, at test relative to extinction. In separate studies, alcohol delivered via intraperitoneal injection either 24 h before or immediately before a test session failed to reinstate CS-elicited port entries, despite producing detectable levels of alcohol in the blood. Conclusions. These results provide new evidence of spontaneous recovery in a Pavlovian conditioning procedure with alcohol as the US. Intriguingly, they also show that both alcohol and water serve as effective triggers for reinstatement. Ongoing studies will test the hypothesis that increasing the discriminability between alcohol and the control liquid during unsignaled exposure will induce an alcohol-specific reinstatement effect at test.

Lin D *The neural mechanism of aggressive motivation*
Social actions, like sex or aggression, may be preceded by a motivated internal state that promotes animals to seek out opportunities to perform these behaviors. While significant progress has been made indentifying neural substrates that are involved in social action, it has been more difficult to assess the neural mechanisms of these underlying motivated or seeking states. The hypothalamus, and in particular the ventromedial hypothalamus, ventrolateral area (VMHvl), now has an established role in intermale aggression. Stimulation of this area promotes attack and neurons in this area are active during aggressive action. We have recently expanded the role of this area to be critical for flexible "proactive" aggression-seeking behavior. Using a social-operant task, where male mice can seek out brief and repeated attack opportunities, we find that single neurons in the VMHvl respond during this motivated seeking phase in addition to the social action phase, and changes in population activity recorded using fiber photometry track changes in task learning and extinction. Optogenetic stimulation of this area accelerates trial-to-trial response

initiation latency, promoting changes in moment-to moment aggressive motivation. In addition, we find a new role for an anatomically segregated population of inhibitory neurons on the lateral edge of the VMHvl (the VMHvl "shell"). These neurons send strong direct inhibitory current to VMHvl neurons and population recording of these neurons shows that activity is decreased during aggressively motivated seeking behavior. Consistent with this, optogenetic inactivation of these GABAergic neurons is also sufficient to accelerate trial-to-trial aggression seeking behavior. Lastly, we used in vivo FRET photometry to detect changes in chloride concentration in the VMHvl during aggression seeking behavior and found that inhibition to this area is reduced during the motivated seeking phase. Together these data suggest that local hypothalamic inhibitory input to the VMHvl behaves as a permissive gate during aggression seeking behavior and the strength of this input is relaxed as animals prepare for and seek out future aggressive action.

Ludwig RJ, Kwon KY, Welch MG *Pavlovian Conditioning: It's MORE than you think it is*

In his 1988 paper, Pavlovian conditioning: It's not what you think it is, Rescorla argued that Pavlovian conditioning was not the simple, relatively unimportant learning process it was generally regarded as by researchers at the time. He held that there was potential for the "conditioned stimulus" to modulate and control emotional behavior through the individual's central nervous system via operant conditioning mechanisms. In this thinking, the properties of the conditioned stimulus itself, including the environment, must be considered as they affect the response. Rescorla proposed that Pavlovian conditioning was critical in the development of neurotic behaviors and emotional disorders, which were studied by the bourgeoning field of cognitive neuroscience. As a result of his efforts, along with others, Pavlovian conditioning remains largely in the service of cognitive neuroscience to this day. In this poster, we will argue that Pavlovian conditioning is misunderstood from a theoretical perspective and underappreciated as a mechanism for preventing and overcoming emotional, behav-

ioral and developmental disorders. We examine the origins of Pavlovian conditioning, starting with the seminal work of Pavlov and other Russian researchers, and continuing through Pavlov's disciple and American champion, W. Horsley Gantt. Gantt's work on conditional neuroses in dogs is reviewed, as well as his theory of the "Effect of Person". We trace the arguments of Pavlovian "functionalists", such as Hollis, Tinbergen and Domjan, who emphasized the importance of studying animals in their natural environment, and examining the unconditional, as opposed to the conditional, stimulus in primal matters involving survival and adaptation. The functional perspective of Pavlovian conditioning takes into account the interaction of the environment of the unconditioned stimulus and particularly looks at how the response changes over time. In so doing, the learning process occurring through Pavlovian conditioning can be assessed in terms of its adaptive significance. Finally, we review Calming Cycle Theory, which proposes a radically new interpretation of Pavlovian conditioning, one that emphasizes its conserved mechanistic role in foundational autonomic learning of emotional behaviors and socialization. In this view, the autonomic states of mother and infant serve as unconditional stimuli that trigger conditional behavioral reflexes. Close physical proximity of a mother and infant dyad that is "emotionally connected" triggers an attraction reflex, and one that is "emotionally disconnected" triggers reflexive avoidance or withdrawal reflex. According to the theory, the goal should be to achieve co-regulation, not self-regulation of autonomic states. We argue that Pavlovian conditioning has been misguided, as research has been aimed at brain mechanisms and interventions based on operant learning. Rather, focus should be redirected to examining autonomic nervous system mechanisms and interventions that benefit from conditional Pavlovian reflexes.

Luyten L, Beckers T *A preregistered, direct replication attempt of the retrieval-extinction effect in cued fear conditioning in rats*
In 2009, Monfils and colleagues proposed a behavioral procedure that was said to result in a permanent attenuation of a previously es-

tablished fear memory, thereby precluding a possible return of fear after extinction (Science 2009; 324:951-5). By presenting a single retrieval trial one hour before standard extinction training, they found an enduring reduction of fear. The retrieval-extinction procedure holds great clinical potential, particularly for anxiety patients, but the findings are not undisputed, and several conceptual replications have failed to reproduce the effect. These failures have largely been attributed to small procedural differences. This preregistered study is the first endeavor to exactly replicate three key experiments of the original report by Monfils and colleagues, thereby gauging the robustness of their seminal findings. Despite adhering to the original procedures as closely as possible, we did not find any evidence for reduced return of fear with the retrieval-extinction procedure relative to regular extinction training, as assessed through spontaneous recovery, reinstatement and renewal. Behavior of animals in the control condition (extinction only) was comparable to that in the original studies and provided an adequate baseline to reveal differences with the retrieval-extinction condition. Our null findings indicate that the effect sizes in the original paper may have been inflated and question the legitimacy of previously proposed moderators of the retrieval-extinction effect. We argue that direct experimental evaluation of purported moderators of the retrieval-extinction effect will be key to shed more light on its nature and prerequisites. ERC Consolidator Grant 648176 (to Tom Beckers)

Luyten L, Luyck K, Gabriëls L, Nuttin B *Electrical stimulation in the bed nucleus of the stria terminalis reduces anxiety in rats and patients*

The bed nucleus of the stria terminals (BST) is an intriguing brain region implicated in stress and anxiety responses. In particular, it has been put forward as a key area in the expression of sustained fear in response to temporally unpredictable threat in rats. Additionally, several neuroimaging studies indicate a role in threat monitoring and anticipation of aversive events in human subjects. Here, we present evidence for anxiety-reducing effects of high-frequent, electrical stim-

ulation in the BST, both in fear-conditioned rats and in psychiatric patients. In a series of preclinical studies, we compared the effects of bilateral electrical stimulation, electrolytic lesions or a sham condition in rats that were previously conditioned to a context using unpredictable shocks. Upon re-exposure to this context, we found that electrical stimulation reduced contextual freezing and startle potentiation, but not to the same extent as lesions. Neither lesions nor stimulation of the BST affected motor behavior or thigmotaxis in an open field test. In a clinical trial with 24 treatment-resistant obsessive-compulsive disorder patients, we found that continuous deep brain stimulation in the BST was safe and significantly decreased long-standing obsessions, compulsions, as well as anxiety symptoms. We conclude that electrical stimulation in the BST may be a promising therapeutic option for otherwise treatment-resistant anxiety patients. Research Foundation—Flanders Project G0C9817N and the Medtronic Chair for Stereotactic Neurosurgery in Psychiatric Disorders at KU Leuven

Madsen HB, Kim JH *Sex differences in the ontogeny of memory - A double dissociation between extinction and infantile amnesia*
Over the years an extraordinary amount of progress has been made in our understanding of the mechanisms of learning and memory. In contrast, much less is known about spontaneous forgetting. Understanding the neurobiological basis of forgetting is relevant for diseases such as Alzheimer's disease, which is characterised by pathological forgetting, and also post-traumatic stress disorder, which involves an inability to forget a traumatic experience. Most of what we understand about the neurobiological basis of forgetting has arisen from studies of infantile amnesia, which describes the accelerated forgetting that occurs during infancy. Infantile amnesia is experienced by most adults as demonstrated by their inability to recall early childhood experiences (prior to the age of around 3). However infantile amnesia is not unique to humans, and most of the research investigating this phenomenon has been performed in rodents using fear conditioning. From these studies, it appears that the protracted development of a number of brain regions and neurotransmitter systems

that are important for learning and memory are likely to underlie accelerated forgetting in juveniles. Preliminary data from our laboratory also suggests that there are sex differences in infantile amnesia, with female juvenile rats forgetting more over time. This is in contrast to recall of fear memory after extinction, where male juvenile rats forget fear memory once extinguished, whereas female juvenile rats do not. This dissociation may be due to differences in the sequence of hippocampal maturation in males and females.

Mahmud A, Cossette M-P, Lay BPP, Esber G, Iordanova M *VTA Dopamine Transients Reduce Prediction Error about Aversive Outcomes*

Learning depends on our ability to predict the future. If our predictions are correct i.e. there is no prediction error, then no further learning is necessary. In the lab, this can be modelled using the blocking paradigm. In blocking, the presence of a good predictor for an outcome prevents learning about other novel cues and the same outcome. Dopamine (DA) in the Ventral Tegmental Area (VTA) has been implicated in prediction error about rewarding events such that the greater the DA the greater the prediction error and thus the greater the increments in learning. However, reduction in DA transmission at VTA target sites (nucleus accumbens and amygdala) have shown a similar effect i.e. increase in prediction error and increase in learning but about aversive outcomes. Here we dought to determined the role of VTA DA in prediction error in fear. We used the Th:cre rats line in conjunction with cre-dependent channelrhodopisn viral vector to show that inducing a dopamine transient at time of an expected footshock in a blocking paradigm augmented the blocking effect i.e. further decreased prediction error and retarded learning about the novel cue. Further, by stimulating nucleus accumbens terminals, we show that this effect is regulated by the VTA-nucleus accumbens pathway. These data show that VTA DA transients have an opposing effect in fear to that in reward, and suggest a possible valence-specific prediction error mechanism. NSERC, CRC Tier 2

Malvaez M, Shieh C, Murphy MD, Greenfield VY, Monbouquette HG, Wassum KM *Amygdala-cortical circuits in reward value encoding and retrieval*

The value of an anticipated reward is a primary consideration in the decision to engage in its pursuit. This value is encoded when the reward is experienced in a relevant motivational state. The basolateral amygdala (BLA) is required for this incentive learning process. But whether it also participates in retrieving this information and how it achieves these functions within the broader reward-seeking circuitry is unknown. Using electoenzymatic glutamate biosensors, we first found that glutamate is transiently released in the BLA during reward value encoding as well as immediately preceding bouts of subsequent value-guided reward-seeking activity. Pharmacological manipulations confirmed the necessity of BLA glutamate receptor activation for both positive reward value encoding and subsequent value-guided reward seeking. The BLA receives dense glutamatergic innervation from several cortical regions, including the orbitofrontal cortex (OFC), a region itself implicated in value attribution. To determine whether OFC afferents to the BLA mediate reward value encoding and/or retrieval, we next used chemogenetic and optogenetic approaches to bidirectionally modulate the activity of these projections, separating the anatomically distinct medial and lateral OFC subregions. Activity in lateral OFC to BLA projections was found to be both necessary for and sufficient to enhance positive reward value encoding, but not for subsequent retrieval of this information for online decision making. Conversely, medial OFC to BLA projections were not required for incentive learning, but were found to be necessary for reward value retrieval and activity in these projections was sufficient to enhance value-guided reward seeking actions online. These data demonstrate that the BLA participates in both the encoding and retrieval of reward value via excitatory input from the OFC and that there is a double dissociation of the contribution of lateral vs. medial OFC to BLA projections to encoding vs. retrieval, respectively. These data have important implications for the myriad diseases marked by maladaptive reward valuation and decision making.

Marton TM, Han E, Hussain Shuler MG *Animals Shouldn't and Don't Use A Temporal Difference Reinforcement Algorithm to Learn How to Spend Time: A Comparison to Novel Alternative Reward-Optimizing Algorithms.*
We identify algorithms that would optimize reward rate for three types of temporal decision making. We compare these algorithms to the policies that would be achieved through temporal difference reinforcement learning. In particular, we derive a novel, normatively-optimal equivalent immediate subjective value function for delayed reward. We also identify the equivalent immediate subjective value function that would be observed were animals to apply a temporal difference reinforcement learning algorithm. We find that these functions have similar forms, but nevertheless exhibit notable differences in expected behavior. We also describe new value variables that can enable optimal temporal decision-making when delays to reward are randomly distributed. These value variables exhibit advantages in learnability, flexibility, and optimality compared to the values that would be learned by temporal difference reinforcement learning. We suggest a novel neural mechanism by which the normatively-optimal functions are executed, which can lead to misestimations and suboptimalities. This novel mechanism's pattern of expected behavior explains ubiquitous but previously mysterious ambiguities in a large historical literature regarding animals' temporal decision making.

Meyer HC, Amelio P, Lee FS *Influences of adolescent cued and contextual fear representations on safety learning*
Anxiety disorders are highly prevalent in developing populations, with diagnoses peaking during adolescence. Unfortunately, conventional behavioral treatments that are based on principles of fear extinction learning, such as cognitive behavioral therapy, are ineffective for a notable percentage of the adolescent population. Thus, an understanding of the development of fear acquisition and regulation is necessary to optimize alternate behavioral treatments better suited for this period. During extinction, a 'safe' memory does not overwrite

the initial threat association, but rather inhibits its expression. This associative competition may render adolescents particularly vulnerable to fear regulation failures. Our lab has recently carried out a series of studies investigating the ontogeny of fear regulation in adolescent mice using 'safety signal' training, where mice are exposed to a stimulus predicting the explicit absence of an aversive outcome. Over time, this stimulus develops 'safe' properties capable of modulating fear responding through a process referred to as conditioned inhibition. Our data show that adolescent mice (postnatal day/PND 29) exhibit limited safety learning (i.e., minimal reductions in freezing behavior when fear and safety signals are presented in compound) when fear and safety signals are trained in parallel. This may result from associative interference, exacerbated by heightened levels of cued fear that our laboratory has previously shown to peak during adolescence. To address this, we exposed mice to fear and safety signals that were separated by both day and context, and found this protocol to enhance safety learning in adolescents. The present data replicate evidence from our lab showing a window of contextual fear suppression specific to adolescence, and suggest a potential interaction between contextual fear and the efficacy of learning about stimuli in service of fear regulation. Taken together, our data indicate that adolescent fear responses towards both discrete cues as well as contexts are important factors to consider when designing laboratory training paradigms in rodents and have practical implications for clinical interventions that may target adolescent anxiety.

Miller DP, Latham H, Cook-Snyder DR, Servatius RJ *Partially reinforced signaled lever press conditioning reveals differences in the expectation versus the presence of shock in behaviorally inhibited Wistar-Kyoto rats compared to Sprague Dawley rats*

It has been demonstrated repeatedly that the behaviorally inhibited Wistar-Kyoto (WKY) strain acquires signaled lever-press avoidance more rapidly and is resistant to extinguishing the avoidance response when compared to Sprague Dawley (SD) rats (e.g., Servatius et al, 2008). Recently it was demonstrated that learning in behaviorally

inhibited humans was less affected by partial reinforcement during Pavlovian eye blink conditioning (Allen et al., 2014). In the present study we compared avoidance acquisition in female WKY versus female SD rats receiving either 100% paired tone-shock trails, or 50% paired trials with 50% tone only trials. Both WKY groups showed higher levels of acquisition compared to either SD group. In fact, SD rats receiving 50% paired trials adopted a strategy of waiting for the first shock pulse and making an escape rather than an avoidance. In contrast, WKY rats receiving 50% paired trials showed high levels of avoidance, even on trials that were consistently not paired with shock (e.g., the first trial of each session). These observations were supported by differential levels of zif activation in the primary somatosensory cortex between the groups. Further, both WKY groups made significantly more non-reinforced lever presses during the intertrial interval. Our results suggest that female WKY rats are driven by the expectation of shock, even when the shock is inconsistent. In contrast, female SD rats are driven by the presence of shock, especially when the shock is inconsistent. These differences in drive could explain why we see enhanced associative learning in human populations that are vulnerable to the development of anxiety and stress disorders.

Miller LA, Heroux NA, Stanton ME *Mechanisms of contextual fear conditioning in pre-weanling and adolescent rats*

The context preexposure facilitation effect (CPFE) consists of three distinct phases—preexposure, training, and testing—in which learning the context, formation of the context-shock association and retrieval of the context-shock association are separated by 24 hours. In contrast, in standard contextual fear conditioning (sCFC), learning of the context and formation of the context-shock association occur in the same training session. In the CPFE, both post-shock and retention-test freezing develop between Postnatal Day (PD) 17-24 in the rat (Jablonski et. al., 2012; Schiffino et. al., 2011). In sCFC, post-shock freezing emerges around PD 18 and retention freezing emerges between PD 17-24 (Rudy & Morledge, 1994; Schiffino et

al., 2011). In adult rats, disrupting basolateral amygdala (BLA) activity or plasticity during training on sCFC impairs both post-shock and retention freezing (Maren et al., 1996). This manipulation on the training day of the CPFE disrupts retention freezing but effects on post-shock freezing are unknown (Matus-Amat et. al., 2007). Experiment 1 compares the developmental profile of sCFC and CPFE using both post-shock and retention measures. Experiment 2 extends the current BLA literature from adult to adolescent rats and to the role of BLA in post-shock freezing during the CPFE. In the first study, PD 17 and PD 31 rats run through either sCFC or the CPFE and were tested for both post-shock and retention freezing. PD31 rats showed robust contextual fear on both tasks and freezing measures relative to nonassociative controls. In contrast, PD 17 rats only showed post-shock but not retention-test freezing during sCFC and failed entirely to perform the CPFE. Inthe second experiment, intra-BLA infusions of muscimol prior to the training day of the CPFE disrupted both post-shock and retention freezing in PD31-33 rats. Our findings suggest that the ontogeny of context conditioning reflects changes in long-term retention of context representations rather than encoding of fear in the amygdala. They also suggest that the BLA plays a similar role in the CPFE in both adolescent and adult rats. Future experiments will extend this comparison to pre-weanling rats.

Miller RR *Symposium: Associative Interference in Acquired Behavior*
Associative interference is a widely studied phenomenon, but it's role in Pavlovian learning is often overlooked. First, Miller will provide a broad framework for the centrality of associative interference in attenuating Pavlovian performance. Then Rosas will discuss circumstances in which associative interference can facilitate new learning by increasing overall attention. Finally, Bouton will generalize beyond S-S learning by focusing on extinction of instrumental learning as a specific instance of associative interference.

Miller RR, Polack CW *Associative Interference as a Major Source*

of Forgetting in Pavlovian Conditioning and the Fate of Forgotten Associations
Associative interference is conventionally viewed as but one of at least four major sources of forgetting of encoded information following successful target acquisition. We will review evidence that associative interference in fact plays a role in memory failure in many situations that are not ordinarily viewed as instances of associative interference (i.e., spontaneous decay, poor match of encoding/retrieval cues, and displacement from working memory). The interfering associations are often subtle in these instances. A taxonomy of associative interference paradigms will be presented. We will then consider the fate of forgotten memories across this taxonomy, concluding that many if not all of these instances of forgetting are reversible as evidenced by their recovery without further relevant training. This perspective suggests that memory failures most commonly arise from retrieval failure as opposed to an irrevocable loss of memory.

Mohammadmirzaei N, Della Valle R, Knox D *Traumatic stress alters neural activity during fear and extinction learning and memory in non-relay thalamic nuclei*
Trauma exposure can lead to psychiatric disorders such as post-traumatic stress disorder (PTSD), which is characterized by persistent fear and anxiety. Basic science studies that characterize neural circuits and molecular processes through which traumatic stress leads to changes in emotional reactivity have focused on neural substrates in cortical and limbic systems (e.g. amygdala, prefrontal cortex, hippocampus). A recent set of studies have identified non-relay nuclei in the thalamus that are critical for emotional memory. However, the effects of traumatic stress on neural activity in these non-relay thalamic nuclei have not been characterized. In this study we examined the effects of single prolonged stress (SPS, rodent model of traumatic stress) on c-Fos and c-Jun expression in the medial habenula, paraventricular thalamic nucleus, rhomboid nucleus, and nucleus reuniens at baseline, fear conditioning, extinction training, and extinction testing. Preliminary findings suggest that SPS exposure

in rats had no effects on baseline c-Fos levels in any thalamic nucleus. During fear-conditioning there was enhanced c-Fos levels in all rats, which decreased during extinction training and testing. SPS decreased c-Fos expression in the rhomboid nucleus during fear conditioning, extinction training and extinction testing. SPS enhanced c-Fos in the paraventricular nucleus and medial habenula during extinction training, and enhanced c-Fos expression in the medial habenula and nucleus reuniens during extinction testing. These findings suggest that traumatic stress exposure can alter neural activity in non-relay thalamic nuclei specifically during fear and extinction learning and memory.

Moulton E, Chamness M, Knox D *Examining the effects of single prolonged stress on glucocorticoid receptor internalization in emotional circuits in the brain*

Changes in glucocorticoid receptor (GR) expression occurs in mood and anxiety disorders such as depression and post traumatic stress disorder (PTSD). GRs are ligand-gated transcription factors that internalize from the cytoplasm to the nucleus when activated. GR expression is enhanced in PTSD patients and has been linked to PTSD symptoms. Yet, the role of trauma-induced changes in GR function within emotional circuits in PTSD is unclear. Single prolonged stress (SPS) is a rodent model of PTSD. Previous studies have demonstrated that SPS enhances GR expression within emotional circuits and that changes in GR activity during fear conditioning affect persistent fear expression in the SPS model. Thus, the SPS model can be used to examine how traumatic stress-induced changes in GR internalization lead to persistent fear expression. In this study, we examined changes in GR internalization in the medial prefrontal cortex (mPFC), dorsal hippocampus (dHipp), ventral hippocampus (vHipp), and amygdala (Amy) using western blot electrophoresis. These brain regions were selected because they are critical for emotional regulation and/or reactivity. Groups of SPS and non-stressed rats were fear conditioned and then euthanized immediately, 30 minutes, or 60 minutes after the end of fear conditioning. Subsets of rats were also eu-

thanized after immediate removal from the housing colony in order to establish basal levels of GRs in the cytoplasm (cy) and nucleus (nu). Preliminary findings suggest that SPS enhances baseline cyGR in the dHipp and prevented an increase in cyGR, relative to baseline, after fear conditioning. These findings are consistent with enhanced GR internalization in SPS rats. However, there was no corresponding increase in nuGR in the dHipp of SPS rats. There was also no effect of fear conditioning on cy or nu GR in the dHipp. Neither fear conditioning nor SPS altered cyGR or nuGR expression in the vHipp. While the study is ongoing, the results support the hypothesis that SPS alters GR dynamics in the dHipp during fear conditioning though this effect is complex.

Mueller I, Brinkman AL, Sangha S *Juvenile pre-exposure to fear, safety or reward cues affects discriminatory conditioning in adulthood* Depending on the appetitive or aversive events that co-occur with initially neutral stimuli, these stimuli can gain positive or negative emotional load; e.g., danger-predictive stimuli elicit fear, while reward-predictive stimuli induce approach behaviour. Both behavioural domains are influenced by safety cues, signalling the non-occurrence of a threat. Typical animal models focus on only one behavioural domain, thereby neglecting a potential interaction. Recently a discriminatory conditioning paradigm was developed that accounts for this shortcoming by integrating all three cues in one paradigm (Sangha et al., 2013). In psychiatric conditions the balance between these behavioural domains and underlying brain structures are disturbed, leading to anxiety disorders and/or addiction. In this study, we thus aimed at modulating this balance through a domain-specific pre-condition to the fear-, reward-, or safety cue (juv-F, juv-R, juv-S) during juvenility, a stress-sensitive developmental period, followed by discriminatory conditioning during adulthood. We hypothesized that preconditioning would strengthen the respective domain and modulate the interaction with other domains during adulthood. Juvenile fear conditioning resulted in an initially increased adult fear response, but was not distinguishable from the control group at the end of the fear

conditioning training. Moreover, unlike the juv-R and juv-S groups, juv-F rats were able to suppress fear in the presence of a safety cue, similar to control rats. Our preliminary results indicate specific consequences depending on the domain preconditioned in juvenility and a beneficial effect of moderate juvenile fear conditioning on later memory specificity. I. Mueller is supported by the Alexander von Humboldt-Foundation.

Myers KP, Brunick AJ, Gerber RB, Kim ES *The 'cue ubiquity paradox' in overeating: conditioned food seeking elicited by unreliable food cues in lean and obese rats*

Environmental cues that predict the arrival of palatable food can become powerful conditioned elicitors of appetite, promoting food seeking and overconsumption even in sated animals. It is frequently argued that the sheer number and ubiquity of such food-paired CSs (advertisements, logos, packages, locations, etc.) in the modern environment elicit a maladaptive degree of conditioned appetitve responding, a major factor driving overeating. However, the literature on cue-potentiated feeding and conditioned meal initiation has not addressed a dilemma we call the "cue ubiquity paradox." In actuality, in the modern food environment food cues are in fact so ubiquitous that, for most people, the majority of routine encounters with these stimuli are actually not paired with eating. From the perspective of conditioning theory, this presents a problem for the straightforward interpretation that such stimuli could become powerful conditioned cues. Following this rationale, we have begun studying individual differences in responsiveness to cues that are only weak or unreliable predictors of food. We adapted a paradigm commonly used to study cue-potentiated feeding which uses distinct auditory/visual cues: a CS+ predicting food delivery and a CSâĂŞ unpaired with food, as well as a third, unreliable CS which predicts food only one-third of the time. In subsequent tests for cue-elicited appetitive responding under sated conditions, we find that lean rats do not respond to the unreliable CS, whereas rats maintained on a high-fat/high-sugar diet respond to the unreliable CS at almost the same level as the CS+.

While several mechanistic explanations for this effect remain to be explored, we argue from this finding that it is not simply the ubiquity of food cues in the modern environment, but rather a tendency to over-respond to weakly-predictive cues that may be a crucial factor in modern environmentally-induced overeating.

Nasser HM, Lesser EN, Lafferty DS, Bacharach SZ, Calu DJ
Role of dissociable basolateral amygdala pathways in sign- and goal-tracking behaviors
Previously observed individual differences in behavioral flexibility of sign- and goal-trackers may be rooted in the recruitment of dissociable basolateral amygdala (BLA) pathways known to mediate behavior that relies on stimulus-response versus stimulus-outcome associations. Here, we sought to determine the extent to which communication of associative information between BLA and anterior portions of insular cortex (IC) supports ongoing Pavlovian conditioned approach behaviors in sign- and goal-tracking rats, prior to manipulations of outcome value. We hypothesized that the BLA mediates goal-, but not sign-, tracking approach through interactions with the IC, a brain region involved in supporting flexible behavior. We first trained rats in Pavlovian lever autoshaping to determine their sign- or goal-tracking tendency. During alternating test sessions, we gave unilateral intracranial injections of vehicle or a cocktail of gamma-aminobutyric acid (GABA) receptor agonists, baclofen and muscimol, unilaterally into the BLA and contralaterally or ipsilaterally into the IC prior to reinforced lever autoshaping sessions. Consistent with our hypothesis we found that contralateral inactivation of BLA and IC increased the latency to approach the food cup and decreased the number of food cup contacts in goal-trackers. While contralateral inactivation of BLA and IC did not affect the total number of lever contacts in sign-trackers, this manipulation increased the latency to approach the lever. Ipsilateral inactivation of BLA and IC did not impact approach behaviors in Pavlovian lever autoshaping. These findings suggest that communication between BLA and IC maintains a representation of the initially learned appetitive association that commonly supports

the initiation of Pavlovian conditioned approach behavior regardless of whether it is directed at the cue or the location of reward delivery. Next, we aim to characterize the real-time neural activity of BLA-NAcC and BLA-IC/OFC projection neurons in ST and GT rats. We use an antidromic optical phototagging approach, in which we express channelrhodopsin (ChR2) in BLA and optically stimulate BLA terminals in NAcC or IC/OFC after recording BLA single unit activity during CS+/CS- discrimination and/or reversal procedures. Offline waveform, frequency, and collision testing of antidromic and spontaneously evoked spikes verifies identification of BLA-NAcC and BLA-IC/OFC neurons in awake, behaving rats. We currently apply this methodology to optically probe and record from both BLA pathways during CS+/CS- discrimination and/or reversal procedures. Together these studies will test our hypothesis that individual differences of ST and GT rats are mediated by activation of dissociable BLA projections to the NAcC and to IC/OFC.

Nelson B, Nelson E, Horenstein K, Edwards A, Lipatova O, Campolattaro MM *The impact of fornix lesions on tone-on-trace and tone-off-delay eyeblink conditioning*

The present study examined if hippocampal fimbria-fornix damage affects tone-on-trace and tone-off-delay eyeblink conditioning in rats. Both types of conditioning include a 500 msec "gap" between the offset of a tone stimulus and the onset of a 25 msec periorbital shock stimulus. The tone presented during tone-on-trace sessions only occurred for 250 msec prior to the gap period on each trial, whereas the tone was continuously played in the background during tone-off-delay sessions and was only interrupted by the gap period on each trial. Half of the rats in each conditioning group (tone-on-trace and tone-off delay) received electrolytic lesions of the fornix and the other half (control rats) were given a sham surgery. Approximately one week after recovery, all rats were trained for ten sessions (one 100 trial-session/day). We found that lesioned rats showed a lower percent of conditioned eyeblink responses compared to control rats for both types of conditioning. Our results suggest that a common neural

pathway is used to acquire tone-on-trace and tone-off-delay eyeblink conditioning.

Ng KH, Sangha S *Neuronal encoding of fear, safety, and reward cue discrimination in the infralimbic cortex*

The continuous expression of 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 are important in rescuing the organism from that immobilizing state to resume exploratory behaviors. Previous studies have shown that the infralimbic (IL) cortex is critical for fear extinction consolidation (Milad & Quirk, 2002 Nature), fear extinction recall, and fear/safety discrimination (Sangha et al., 2014 Neuropsycopharm). IL neurons also show cue-elicited activity during the recall of fear extinction memory. The magnitude of the increase in tone elicited responses in the IL is proportional to fear extinction performance in rats (Milad & Quirk, 2002 Nature). We hypothesized that IL neurons also encode safety information that is critical for fear suppression behavior. We recorded neurons from the IL using multi-array electrodes and trained rats in a fear-safety-reward discrimination paradigm that is well established in our laboratory (Sangha et al., 2013 J Neurosci; Sangha et al, 2014 Neuropsychopharm; Sangha et al., 2014 Frontiers Beh Neuro). Rats in this task learn a fear cue predicts a mild footshock, a safety cue does not predict footshock, and a reward cue predicts sucrose delivery. When the fear and safety cues are presented simultaneously and not paired with footshock, rats learn to suppress their fear response when compared to the fear cue+shock condition. Our preliminary multi-unit data show that IL neurons increase in firing from baseline to the combined fear+safety cue compared to either the safety cue or fear cue presented alone. Some of these neurons also showed an increase in firing to the reward cue. Together, these data suggest that increased IL activity during the fear+safety cue may be contributing to the suppressed fear behavior, indicating the IL may be specifically engaged during potentially fearful situations in order to actively regulate fear responding. Our data also suggest that the IL may contain

a network of neurons encoding safety and reward together.

Norris MR, Greiner E, Mueller I, Ng KH, Sangha S *Sex differences in suppression of conditioned fear during a safety cue in a fear-safety-reward cue discrimination task*

The inability to distinguish safety from fear is a biomarker of Post-Traumatic Stress Disorder (PTSD) and has damaging effects on everyday functioning. Despite the higher diagnosis of PTSD in women, research using female rats has been lacking. A recent experiment discovered that female rats exhibit another fear behavior, quick "darting" movements (Gruene et al, 2015). We examined how sex-mediated fear behavior in male and female rats differ during safety signal learning to test the hypothesis that females will show a different fear behavior profile compared to males during this learning. Male and female rats underwent four discriminative cue sessions (DC). During DC, rats were exposed to four cues: fear (tone A), safety (light), fear+safety (tone A+light), and reward (tone B). The reward cue was paired with sucrose and the fear cue was succeeded by a mild 0.5mA footshock, whereas the safety and the fear+safety cues were not. The fear and safety cues (tone A, light) were counterbalanced and shock sensitivity levels were compared in male and female rats. Time spent freezing, darting and reward seeking were quantified. Our data show females (n=20) exhibit equitable levels of freezing to the fear and fear+safety cues, indicating a lack of suppression of conditioned fear during a safety cue. In contrast, male rats (n=16) do show suppression of conditioned fear in the presence of the safety cue. Additionally, early in DC training female rats exhibited significantly higher reward seeking behavior during the reward cue, suggesting they are more reward responsive. Differences in female rats' learning of safety and reward signals suggest the need for research on the underlying neurobiological processes, which may lead to gender-specific treatment techniques for disorders involving anxiety and/or addiction.

Odynocki N, Poulos AM *Pavlovian Fear Conditioning: The Behavioral and Neuroanatomical Effects of Recent and Remote Memory in*

Between- and Within-Subject Designs

Contextual fear memories in adult animals can persist across an extended period of time. Prior studies have demonstrated this persistence of context fear remains can remain stable or incubate across recent and remote intervals. Research aimed at identifying the neural systems supporting recent and remote contextual fear memories have demonstrated a functional role of the hippocampus, prefrontal cortex, and basolateral amygdala. However, some studies assert that the hippocampus is involved in temporary storage of context fear memories, while others postulate the hippocampus plays a permanent role. These disparate conclusions concerning the behavioral and neural mechanisms underlying incubation warrant further investigation. In the present study, we utilized adult male C-57BL/6J mice in two Pavlovian context fear conditioning experiments to examine the relationship between context fear incubation and the neural activity within dorsal hippocampus (proximal-distal CA1, CA3, dentate gyrus), basolateral amygdala (lateral, anterior, posterior nuclei) and prefrontal cortices (anterior cingulate, prelimbic and infralimbic). We analyzed the expression of the immediate early gene c-Fos across the rostral-caudal extent of these brain regions matched to plate levels of the Allen Mouse Brain Reference Atlas. Mice were divided into 3-shock, no-shock or home-cage conditions. In the first experiment, mice were tested 3 or 28 days following acquisition and sacrificed 90 minutes later. Freezing in the remote group was elevated compared to recent group, confirming incubation. This incubation seemed to be supported by an increase in c-Fos activity in areas within the hippocampus and prefrontal cortex of the 3-shock remote group. To further investigate changes in behavioral expression and c-Fos signaling patterns across time, a within-subject experimental design with repeated testing at recent and remote intervals was conducted. Results initially showed a stable level of freezing across time but further analysis revealed distinct patterns of freezing among animals in the shocked group. C-Fos analysis demonstrated that animals subjected to the context, regardless of shock condition, had consistently greater neural activation than the home-cage control group.

Opendak M, Perry R, Diaz-Mataix L, Santini E, Doyere V, Klann E, LeDoux JE, Sullivan RM *Maternal gating of infant memory consolidation via distinct molecular events in the amygdala*
Conditioned responses to threatening cues change across development. However, the molecular mechanisms underlying these developmental changes remain poorly understood. Pavlovian odor-shock conditioning produces learned preferences in rats younger than postnatal day (PN) 10, while producing learned aversions in older pups. Between PN 10 and 15, maternal presence during learning leads to acquisition of a preference, while pups conditioned alone learn an threat. Here we explore the roles of canonical signaling cascades, such as mTOR and ERK, involved in the consolidation of pavlovian threat memory during a period when learning is dependent on maternal presence. Pavlovian odor-shock conditioning produces learned preferences in rats younger than postnatal day (PN) 10, while producing learned threats in older pups. We observed increased phosphorylation of proteins within the mTOR pathway in animals that learned aversion after PN15; administration of the mTOR inhibitor rapamycin was sufficient to abolish behavioral threat expression. In rats that learned threat through independent conditioning between PN10 and PN15, we observed an increase in the phosphorylation of ERK pathway proteins; inhibition of the ERK pathway abolished threat memory consolidation. Furthermore, the presence of the caregiver or pharmacological inhibition of corticosterone during memory consolidation was sufficient to block ERK-dependent learning in pups younger than PN15. These data suggest that the process of memory consolidation at the molecular level shows gradual developmental shifts that align with behavioral transitions during infancy. F32-MH112232 to MO

Ortiz S, Latkso MS, Jasnow AM *A novel neural circuit promoting fear generalization*
A key characteristic of many anxiety disorders is the generalization of fear responses to neutral stimuli. After context fear conditioning, mice display higher levels of freezing in the training context compared

to a novel context when tested within 24 hours. Over time mice begin freezing to novel contextual cues, suggesting generalization of fear to additional contexts. Our previous research identified several regions that promote this generalization during a remote test, including the ventral hippocampus (vHPC) and the anterior cingulate cortex (ACC); inactivation of these regions restores memory precision and inhibits generalized fear in the novel context. In the current study, we utilize chemogenetics (DREADDs) to investigate the circuit through which the vHPC and ACC promote generalization at remote time points. C57BL/6 mice were stereotaxically infused with either an hM4D(Gi)-expressing virus or a control virus expressing EYFP targeting the vHPC or ACC at 6 weeks of age. After a one-week recovery, we stereotaxically implanted bilateral guide cannulae directed at the basolateral amygdala (BLA). Mice were then give an additional week of recovery before context fear conditioning began. Five minutes prior to the delayed context test (21 days after training), mice were infused with 0.2ÂţL of clozapine-N-oxide (CNO) into the BLA to inactivate the projections from either the vHPC or ACC. Disrupting the projections from either of these regions to the BLA restored memory precision and blocked generalized fear. hM4D(Gi) virus infused mice displayed significantly lower levels of freezing in the neutral context compared to EYFP infused mice and compared to hM4D(Gi) infused mice tested in the training context at 21 days. These data indicate that the ACC and vHPC control generalized contextual fear responses likely through their projections to the BLA. These data are also helpful in understanding the neural processes involved in anxiety disorders characterized by generalized responding.

Pajser A, Gaeddert B, Fisher H, Long C, Kallenberger P, Limoges A, Pickens CL *Operant overtraining increases infralimbic activity in the fear incubation task*

The fear incubation task is an extended training procedure used to cause low fear soon after training that grows over time. However, the neurobiological basis of this effect, particularly the low fear observed soon after training, is unknown. One possibility is that extended train-

ing leads to habituation to the shocks, so that the tone cue is repeatedly paired with ineffective shocks. If so, then the overtraining may lead to an effect similar to extinction, and the low fear seen soon after extended training may be associated with increased neuronal activity in the infralimbic cortex (IL), an area involved in extinction learning. The current study examined whether low fear soon after extended training is associated with increased IL activation, compared with rats given a single day of fear conditioning or no fear training. Male Long-Evans rats acquired lever-pressing and then underwent fear training for 1 or 10 days. During training, while lever-pressing on a VI60 schedule of reinforcement, half of the animals in each group received 10 30-sec tones co-terminating with a 0.5-sec foot-shock pseudo-randomly throughout the 90-min session and half of the animals received the same tones with no shock. Two days later, animals underwent a cued fear test in which fear was measured using conditioned suppression of lever pressing. Brain tissue was extracted 120 min after the beginning of the test and subsequently processed using immunohistochemistry to target c-Fos. As is typical with fear incubation, rats that underwent 10 days of shock exposure exhibited lower fear than those that underwent 1 day of shock exposure. There was no effect of shock on IL c-Fos expression in either the 1 day or 10 day groups. However, both groups that received extended training (10 days) showed higher levels of Fos-positive cells in IL than the limited training (1 day) groups, regardless of whether the tones were paired with shock. Our results suggest that IL activity is not associated with high fear after a single day of fear training, or suppression of fear after extended fear training. However, our results also suggest that the extended lever-press training in our fear incubation procedure leads to increased IL activity (possibly indicating habit formation), and that the increased activity of IL is unaffected by the co-occurring fear training and associated stress. Additional research will be needed to determine whether operant responding in our task would be insensitive to devaluation, and whether habit formation would be affected by co-occurring fear training.

Pan PL, Keiser AA, Tronson NC *Context fear memory retrieval induces sex-specific recruitment of the ventral hippocampus*
In males, dorsal hippocampus has been extensively studied and more recently, ventral hippocampus has also been implicated as a key region in the circuitry underlying context fear memory. In females, however, the precise role of hippocampus and the mechanisms underlying context fear conditioning and retrieval remain less clear. Here we examined the role of, and signaling pathways activated in, ventral hippocampus during retrieval of context fear memory in both males and females. Ventral hippocampus was robustly activated after retrieval of context fear conditioning in both sexes, with females showing greater levels of cFos compared with males. These data suggest a role for ventral hippocampus in retrieval of context fear conditioning in both sexes, but that males and females likely differ in the molecular mechanisms recruited during memory retrieval. To determine whether ventral hippocampus is required for memory retrieval, male and female mice received infusions of muscimol into ventral hippocampus prior to retrieval of foreground context fear conditioning. We observed decreased freezing in both males and females, demonstrating that ventral hippocampus is required for context fear memory retrieval in both sexes. Finally, to identify whether males and females recruit different intracellular signaling pathways, we collected ventral hippocampus one hour after retrieval of context fear and conducted western blot analysis to identify the activation of PKA-CREB-related signaling pathways. Together, our data demonstrate that ventral hippocampus is required for retrieval of context fear, and that retrieval activates different molecular mechanisms in males and females.

Parsons RG, Lee J, Russo AS *Mechanisms by which prior fear conditioning facilitates subsequent fear learning*
Previous experiments from our lab have shown that exposure to a single pairing of light with a weak shock, which alone did not support the formation of a fear memory, primed subsequent learning such that delivery of a second identical trial within a time window that develops by an hour and lasts several days results in a robust long-term

memory. These findings suggest that the initial trial engages a time-dependent priming mechanism that facilitates subsequent learning. In the same study we showed that the priming effect was lost if different cues were used to signal shock on each of the two trials. However, the lack of facilitation between the two dissimilar training trials might reflect the fact that neither trial alone supported memory formation. Here we tested whether or not prior auditory fear conditioning, which alone supports long-term memory, would facilitate subsequent learning to a single trial of light and shock, and if so, what the optimal time intervals are between events that allows for facilitation. Rats were first exposed to either two pairings of a tone with a shock or a single pairing of light and shock. These animals were then given a pairing of light and shock either, 4 minutes, 60 minutes, or 24 hours after the initial training event. We compared these animals to rats which were only given a single paring of light and shock, and memory for the light cue was assessed using fear potentiated startle. Consistent with our prior results a single light shock trial did not support memory, but two trials spaced by either 60 minutes and 24 hours resulted in robust long-term memory. Rats that were first given training with an auditory cue that predicted shock also showed facilitation of subsequent learning when the light-shock trial was presented at both 60 minutes and 24 hours later. Interestingly, in the rats given auditory fear conditioning and a single light-shock trial 24 hours later, there was an inverse relationship between levels of fear to the two different cues such that rats which showed high levels of fear to the noise cue, tended to show lower levels of fear to the light cue and vice versa. This relationship was not observed in animals trained using the other time intervals. This suggests that strong learning of the initial event occludes subsequent learning, and that this mechanism takes longer than 1 hour to develop. Collectively, our findings indicate that prior training events can facilitate subsequent learning for relatively long periods of time, even when the initial and subsequent events are dissimilar.

Polack CW, Craddock P, Wasserman JS, Miller RR *Associative*

chains support second-order conditioning in humans
Second-order conditioning (SOC; i.e., conditioned responding to S2 as a result of S1-US pairings followed by S2-S1 pairings) is generally explained by either a direct S2**CR association or by an associative chain (i.e., S2**ïČăS1 representation**ïČăCR . Previous research found differences in responses to S2 after S1 was extinguished which depended on the nature of the S2-S1 pairings (i.e., sequential or simultaneous). In two experiments with human participants, we examined the possibility that such differences result from S1 evoking S2 during extinction following simultaneous but not sequential S2-S1 pairings. Little evocation of S2 by S1 following simultaneous pairings may have minimized the evoked representation of S2 being paired with absence of the outcome (i.e., mediated extinction). Using sequential S2-S1 pairings, both Experiments 1 and 2 failed to support this account of how extinction of S1 reduced responding to S2. Experiment 1 found that extinguishing S1 reduced responding to S2, while extinguishing S2 had little effect on responses to S1, although forward evocation of S1 during extinction of S2 paired the evoked representation of S1 with absence of the outcome. In Experiment 2, evocation of S2 during S1 nonreinforced trials was prevented because S2-S1 pairings followed (rather than proceeded) S1-alone exposures. Nevertheless, responding to S2 at test mimicked S1 responding. Responding to S2 was high in the context in which S1 had been reinforced, and low in the context in which S1 had been nonreinforced. Collectively, these experiments provide additional support for the associative chain account of SOC.

Pullins SE, Cullen PK, Ferrara NC, Helmstetter FJ *Contributions of the retrosplenial cortex to event-related and contextual fear memory formation in trace fear conditioning*
The ability to form memories for aversive events, as well as for where those events occur, is critical to survival. Recent research suggests a critical role for the retrosplenial cortex (RSC) in the encoding and storage of events and their associated contexts. However, the nature of information processing in the RSC during learning remains

unclear due to previous manipulations of the RSC lacking spatial and temporal precision. Our initial immunohistochemical analysis of the RSC following auditory trace fear conditioning, a paradigm used to model declarative memory in rodents, showed increased neuronal activity throughout its longitudinal extent. While these results suggest that the RSC may be functionally homogeneous throughout its rostral-to-caudal expanse, previous lesion and immunohistochemical work implicates differential function between the anterior and posterior segments. We then used optogenetics to examine specific functions of RSC segments during trace fear conditioning. Rats were transfected with ArchT, under control of the neuron-specific promoter CAG, while control rats received a similar viral cassette that lacked the lightsensitive pump. By injecting these viruses into the anterior RSC (aRSC) or the posterior RSC (pRSC), and then mounting LEDs over a thinned skull window immediately above the site of transfection, we can achieve spatially and temporally precise reductions in neuronal excitability. All rats received light delivery during each learning trial of conditioning. The following days, rats were tested for memory to the tone and to the training context. Silencing of aRSC during each tone-shock pairing impairs memory formation for the training tone, whereas pRSC silencing selectively impairs contextual memory formation. These results suggest that the two poles of the RSC may differentially contribute to event-related and contextual memory formation, and that the RSC may normally aid in the final association of these two distinct aspects of the fear memory. NIH MH069558, NIH MH112141

Ramanathan KR, Jin J, Maren S *Prefrontal-reuniens projections contribute to the acquisition and expression of fear extinction*

Fear extinction is a critical component of behavioral therapies for anxiety- and stress- related disorders. Considerable work has shown that the amygdala and medial prefrontal cortex (mPFC) are crucial for learning fear extinction, whereas the hippocampus (HPC) regulates the context-dependent expression of fear after extinction. Recent evidences have shown that HPC interaction with mPFC is cru-

cial for the expression of fear after extinction. Anatomically there is a unidirectional monosynaptic projection from HPC to mPFC to mediate the same. More recently, various reports have shown that the mPFC is positioned to influence information processing in the HPC via indirect projections through the mid-line thalamic nucleus reuniens (RE). However, it is not known how RE gates the information flow across these two brain regions. To address these questions, we first pharmacologically inactivated RE using Muscimol (GABAA agonist) prior to either extinction or retrieval sessions. We show that inactivation of RE led to deficits in both encoding and expression of extinction memories. To determine if extinction deficits subsequent to RE inactivation were due to blocking PFC input to the RE (and presumably to the HPC), we performed circuit manipulations using Cre-dependent DREADD's (designer receptor exclusively activated by designer drugs) to silence mPFC->RE projections. We found that silencing RE projectors in the mPFC reproduced the extinction deficits we observed after muscimol inactivation of RE indicating that the deficits seen from RE inactivation arises from mPFC. While the studies exploring RE projections to the HPC are ongoing. Overall, these results indicate that the RE may be critical for gating information flow between the mPFC and HPC during extinction.

Ramsaran Al, Nath M, Ahmed M, Josselyn SA, Frankland PW

Perineuronal nets regulate hippocampal memory formation and specificity

The extracellular matrix (ECM) composed of proteins and proteoglycans is a key regulator of plasticity in the central nervous system. In particular, the accumulation of ECM structures known as perineuronal nets (PNNs) during early postnatal development constrains juvenile plasticity and closes critical periods in primary visual cortex and basolateral amygdala (Pizzorusso et al., 2002; Gogolla et al., 2009). Little is known about how PNNs contribute to hippocampal plasticity and memory. To address this, we studied the contribution of PNNs to contextual fear memory in mice. We first characterized the distribution of PNNs in the dorsal hippocampus (sub-

fields CA1, CA2, CA3, dentate gyrus, and fasciola cinereum) of adult mice using immunohistochemistry to identify chondroitin sulfate proteoglycans (CSPGs). Consistent with the role of PNNs in neural circuit inhibition (Lensjo et al., 2017), CSPG-containing PNNs surrounded parvalbumin-expressing (PV+) interneurons in all subfields of the hippocampus and were additionally intermingled with PV+ neurites around CaMKIIα-expressing neurons in CA2 and fasciola cinereum. Given the role of PNN formation in attenuating critical period plasticity, we next quantified the development of PNNs in subfield CA1 of mice from infancy (P16) through adulthood (P60). We observed rapid maturation of PNNs between the second and third postnatal weeks, which corresponded to the same developmental epoch during which mice first began forming specific contextual fear memories. To investigate whether PNNs were necessary for memory specificity, we injected chondroitinase ABC (ChABC) into the hippocampus of adult mice to digest CSPGs, thereby degrading PNNs. Injection of ChABC into CA1 caused rapid depletion of PNNs, but did not prevent PNN regeneration in the weeks following surgery. PNN removal before contextual fear training or retrieval resulted in memory generalization when mice were tested in a neutral context. ChABC injection before training also impaired short- and long-term memory for the training context, but did not alter fear expression to an auditory cue or anxiety-like behaviors in an open field or elevated plus maze. Together, these results demonstrate that PNNs are necessary for hippocampal memory formation and specificity. Ongoing studies will determine the role of PNNs in the encoding and retrieval of hippocampal engrams and whether PNN maturation underlies a developmental critical period for hippocampal memory.

Rankin CH, McDiarmid TA *Identifying the behavioural function of genes and gene networks associated with Autism Spectrum Disorder using C. elegans*

Autism Spectrum Disorder (ASD) is a diverse group of genetic neurodevelopmental disorders characterized by social impairment, repetitive behaviour, and sensory processing abnormalities. This disorder

affects ∼1% of the population, and is often severely debilitating with no broadly successful treatments available. There is a strong genetic component to Autism, however it is not known how genes associated with ASD alter brain and behaviour to lead to the disorder. Although a very large number of mutations in many, many genes have been implicated in ASD it is not clear what all of these genes do, whether any of them interact, and how the mutations contribute to ASD. Thus understanding where, how and when these genes function in living animals may shed light on what causes ASD. Here we use a microscopic nematode round worm, Caenorhabditis elegans to characterize the function ASD-associated genes. C. elegans is easy to genetically engineer, and our automated behavioural scoring system allows us to rapidly and systematically study neurodevelopmental and behavioural effects of mutations in each of the hundreds of genes associated with ASD. Because patients with ASD show habituation deficits we are testing habituation in strains of worms with mutations in the C. elegans orthologs of human genes implicated in ASD. If we find an effect on habituation we are attempting to rescue the deficit with the human gene to show functional homology. Thus far we have characterized morphology, locomotion, and habituation phenotypes for 99 strains of C. elegans covering orthologs of 87 ASD-associated genes. This research has generated a large number of novel genotype to phenotype relationships that range from severe developmental delays and uncoordinated movement to subtle deficits in sensory ability and in habituation. We are currently working with bioinformaticians to cluster our gene data to discover novel gene networks that underlie some of the phenotypes we have found. This research will help us understand what these genes do and how they might contribute to ASD. These studies will also allow grouping genes into those contributing to specific behavioural phenotypes which may allow a greater understanding of the heterogeneous nature of ASD, and identify novel therapeutic targets for treating ASD. Canadian Institute for Health Research and SFARI

Reis DS, Helmstetter, FJ *Sex differences in differential fear con-*

ditioning during the acquisition and consolidation of learned safety
The ability to distinguish between threatening and non-threatening situations requires careful regulation of behavioral and physiological responses to stress and fear. Deficits in fear regulation are maladaptive and can lead to the development of anxiety disorders such as PTSD. Women are nearly twice as likely to develop PTSD as are men and laboratory animal studies have shown facilitated fear acquisition, resistance to fear extinction, deficits in extinction retention and impaired discrimination between danger and safety cues in females. Taken together this suggests a propensity for reduced inhibitory control over fear responding in females. Here we investigate the mechanisms underlying fear discrimination deficits in females using an auditory differential fear conditioning procedure. Our results suggest that fear discrimination depends on successful memory consolidation of the excitatory fear signal as well as the inhibitory safety signal. Female but not male rats showed indiscriminate fear responding to both the fear and safety cue and this may be due to impairments in learned safety by female rats. Together these data suggest that sex differences in the discrimination of fear and safety may be the result of deficits in the consolidation of learned safety in females and further supports the idea that deficits in fear regulation underlie the increased risk of PTSD in females.

Remedios R, Kennedy A, Zelikowsky M, Grewe BF, Schnitzer MJ, Anderson DJ *Social behavior shapes hypothalamic neural ensemble representations of conspecific sex*
All animals possess a repertoire of innate (or instinctive) behaviors, which can be performed without training. Whether such behaviors are mediated by anatomically distinct and/or genetically specified neural pathways remains a matter of debate. Here we report that hypothalamic neural ensemble representations underlying innate social behaviors are shaped by social experience. Estrogen receptor 1-expressing (Esr1+) neurons in the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl) control mating and fighting in rodents. We used microendoscopy to image VMHvl Esr1+ neuronal

activity in male mice engaged in these social behaviours. In sexually and socially experienced adult males, divergent and characteristic neural ensembles represented male vs. female conspecifics. But surprisingly, in inexperienced adult males, male and female intruders activated overlapping neuronal populations. Sex-specific ensembles gradually separated as the mice acquired social and sexual experience. In mice permitted to investigate but not mount or attack conspecifics, ensemble divergence did not occur. However, 30 min of sexual experience with a female was sufficient to promote both male vs. female ensemble separation and attack, measured 24 hr later. These observations uncover an unexpected social experience-dependent component to the formation of hypothalamic neural assemblies controlling innate social behaviors. More generally, they reveal plasticity and dynamic coding in an evolutionarily ancient deep subcortical structure that is traditionally viewed as a "hard-wired" system.

Ressler RL, Goode TD, Maren S *Inhibition of protein synthesis in the dorsal hippocampus prevents reconsolidation of a covertly retrieved fear memory*

Substantial evidence indicates that memories enter a labile state after retrieval, and administration of protein synthesis inhibitors interferes with the reconsolidation of reactivated memories. After fear conditioning, infusion of protein synthesis inhibitors into the amygdala impairs the reconsolidation of fear to an auditory conditioned stimulus. However, it has been reported that indirectly reactivated memories (e.g., memories to a second-order CS) are not sensitive to protein synthesis inhibition in the amygdala. Because the hippocampus is thought to play a role in the S-S associations that underlie higher order conditioning phenomena, we explored whether an indirectly retrieved context memory would be sensitive to protein synthesis inhibition in the hippocampus. It has previously been reported that backward conditioning, a procedure in which the US directly precedes the CS, is mediated by contextual fear (i.e, a CS->[US-context] association). First, to demonstrate that backward conditioning relies on contextual fear,

we tested whether the extinction of fear to the conditioning context selectively attenuates fear to a backward- but not forward-trained CS (Exp. 1; freezing served as the dependent variable). Accordingly, rats were conditioned using either forward (FW; CS-then-US) or backward (BW; US-then-CS) trials (CS = 10 sec, 2 kHz, 80 dB auditory cue; US = 2 sec, 1.0 mA footshock; context A). The following day animals underwent context extinction (context A; no CS, no US) or novel context exposure (context B). Animals were then tested in a new context (C) in the presence of the auditory CS. Results revealed that conditioned fear was selectively reduced in BW-trained animals that received extinction of the conditioning context. In Exp. 2, rats were implanted with bilateral cannulae aimed at the dorsal hippocampus (DH). After recovery, rats were conditioned to a FW or BW CS as in Exp. 1. 24 hrs later, all rats received a single CS exposure in a familiar context (B) to reactivate the memory of the conditioning context. To target reconsolidation of the memory retrieved by the CS, intra-DH microinfusions of the protein synthesis inhibitor rapamycin (or vehicle) immediately followed the retrieval session. 2 days later, contextual fear was examined in a single 20 min exposure to the original conditioning context (A). In support of our hypothesis, BW- but not FW-conditioned animals that received rapamycin post-retrieval showed attenuated context fear. These results provide evidence that CS presentations outside of the original conditioning context can retrieve the contextual memory in BW- but not FW-trained animals, and that the reconsolidation of this indirectly retrieved memory relies on protein synthesis in the DH. This work was supported by grants from the National Institute of Mental Health (R01MH065961 to S.M. and F31MH107113 to T.D.G.), and a McKnight Foundation Memory and Cognitive Disorders Award to S.M.

Reverte I, Jou C, Shur A, Flores L, Iordanova M, Esber G *A self-initiated Pavlovian procedure for in-vivo electrophysiology recording*
Single-unit recording studies in awake, behaving animals require the use of within-subject designs as well as an elevated number (>10) of trials for each trial-type per session. These conditions are often diffi-

cult to meet in Pavlovian conditioning tasks, where better learning is observed with long intertrial intervals (ITIs), unless the total duration of the session is lengthened beyond feasibility. To circumvent this problem, we developed a novel variant of the Pavlovian magazine-approach procedure, which we have dubbed the "self-initiated Pavlovian procedure" (SIPP). Similar to the standard magazine-approach procedure, in the SIPP 10-s CSs are pseudorandomly presented and followed (or not) by a reward delivered to a magazine. Likewise, anticipatory head-entries to the magazine during the CSs are taken as evidence of successful conditioning. However, unlike the standard magazine-approach procedure, where the animal passively receives the CS presentations, in the SIPP it falls upon the animal to initiate the CS. This the animal can do by performing a response (in our case, a nose-poke at an odor-port) upon receiving a cue (a light inside the odor-port) signaling the beginning of each trial. After a trial is completed, a short ITI (5-10 s) follows. The SIPP permits packing 120 trials in a single 2-h session, more than doubling the number of trials achievable in that time with the standard procedure. Additionally, the SIPP ensures that on every trial the animal is engaged, attentive and starts the trial in the same position, all of which are desirable features in single-unit recording studies. NIDA K99-DA036561

Rice BA, Eaton SE, Prendergast MA, Akins CK *A glucocorticoid receptor antagonist reduces sign-tracking behavior in male Japanese quail*

Addiction is characterized as a chronic debilitating disease. One devastating feature of addiction is the susceptibility of relapse (40–60%) after stretches of abstinence. One theory that may account for relapse suggests that drug cues (e.g., paraphernalia) may increase stress hormones, and this may prompt relapse. Repeatedly pairing a neutral cue with a reward is commonly utilized to measure what subjects learn about a cue that is predictive of reward. Research has shown that animals that attend to a cue more than to the reward (sign trackers) may be more vulnerable to drug addiction. Additionally, research has shown that sign tracking is associated with an increase

in corticosterone (CORT) a primary stress hormone. PT 150 is a novel glucocorticoid receptor antagonist that moderates the release of CORT. In the current experiment, it was hypothesized that subjects given repeated administration of PT 150 would reduce sign tracking compared to subjects given placebo. Time spent (sec) at a cue that predicts reward (CS+) served as a measure of sign tracking, and PT 150 or placebo was administered following sign tracking. An independent sampled t-test revealed that subjects that received PT 150 had reduced time spent at the CS+ compared to controls [t (438) =3.549, p <0.05]. Given the devastating effects of drug addiction, identification of a potential pharmacological intervention in the reduction of relapse would be of great value. Therefore, future research is needed to validate the use of PT 150 in reducing behaviors associated with drug addiction.

This authors gratefully acknowledge research support from the National Institute of on Drug Abuse of the National Institutes of Health (under award numbers T32DA03520 awarded to Rush and R01DA025032 awarded to Akins). Authors would like to thank Dr. Lynda Sharrett-Field for guidance in drug administration and measurements, Joshua Beckman for early stage development of procedures, and Palisades Therapeutics, LLC for the generous gift of PT150.

Richard JM, Stout N, Acs D, Janak PH *Ventral pallidal encoding of reward seeking depends on the underlying associative structure*
Activity in ventral striatopallidal circuitry is thought to be a critical mechanism by which previously neutral cues are able to elicit reward seeking following learning. Dopamine inputs to this circuitry play a critical role in this process. Recently we have shown that the activity of ventral pallidum (VP) neurons in response to a cue predicting reward availability encodes both the likelihood and latency of subsequent instrumental reward-seeking actions (Richard et al., 2016). Here, we investigated whether VP cue responses would encode and contribute similarly to the vigor of Pavlovian versus instrumental reward seeking behaviors, when these responses consist of superficially similar locomotor response patterns, and are driven by similar

levels of reward expectancy. During Pavlovian conditioning, male and female Long Evans rats were trained to associate one auditory cue (the CS+) with delivery of 10% liquid sucrose reward (not contingent on the animal's behavior) and alternative auditory cue (CS-) with no delivery of reward. In the instrumental task, one auditory cue (the discriminative stimulus; DS) signaled availability of the same sucrose reward, if the animal made an entry into the reward port during the cue period; the alternative cue (NS) signaled no reward availability. Rats were trained in one of these tasks until they entered the reward port on >70% of reward cue trials (CS+ or DS), and <30% of control cue trials (CS- or NS), and then were implanted with drivable microwire arrays aimed at VP. We found that, similarly to our previous report, cue elicited activity in ∼25% of VP neurons significantly predicts the latency of instrumental reward seeking, even when it consists of a much simpler behavior: entry to a reward port. In contrast, VP encoding of Pavlovian port entry latency did not exceed chance levels. Further, when we assessed the impact of either VP inactivation with GABA agonists, or dopamine blockade, with the non-selective antagonist flupenthixol, we found that only the latency of reward seeking driven by the DS, but not by the CS+, was affected by these manipulations. These results suggest that VP encoding of latency, as well as the functional contributions of both VP activity and dopamine inputs, are not related to trial-by-trial variation in the value of the expected reward, or to motor invigoration more generally, but to the ability of incentive cues to invigorate reward seeking behaviors upon which reward delivery is contingent. Funding was provided by NIH grants AA022290, AA014925, DA035943 and a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation.

Robinson-Drummer PA, Long VS, Stanton, M *Evidence of NMDA-independent acquisition of context memory in adolescent rats*

Acquisition of contextual fear requires NMDA-receptor activation in the rodent brain. However, NMDA-independent learning has been observed during contextual fear re-acquisition (Sanders & Fanselow, 2003; Hardt et al., 2009; Tayler et al., 2011). Juvenile rodents show

NMDA-independent re-acquisition of cued and standard contextual fear conditioning (sCFC) even though they show no memory for the initial conditioning (Li & Richardson, 2013; Chan, Baker & Richardson, 2015). This suggests that fear conditioning in developing animals produces persistent molecular changes regardless of (SIPP). Similar to the standard magazine-approach procedure, in the SIPP 10-s CSs are pseudorandomly presented an memory retention. However, whether incidental contextual learning can be acquired in an NMDA-independent way and at this age is yet to be determined. The current experiment extended these findings to incidental spatial learning in adolescent rats using the context preexposure facilitation effect (CPFE), a variant sCFC that requires NMDA-receptor activity to acquire the representation of the training context. During early adolescence (PD31), animals were or were not exposed to a novel alternate-context (not the CPFE context) only. Five days later, they underwent the CPFE protocol—context preexposure, immediate shock training, context testing, 24 hr apart (PD36-38). Prior to training context preexposure at PD36, animals were given MK-801, an NMDA-receptor antagonist, or vehicle. In controls without prior alternate context exposure MK-801 impaired the CPFE. In contrast, previous alternate context exposure prevented this MK-801-induced learning deficit. These results suggests that incidental learning of a spatial context alone can affect subsequent context learning by inducing lasting changes in NMDA receptor-related systems. Subsequent studies are underway to determine if infant rats will show a transition to NMDA-independent context learning. Alternatively, the separation of context learning from context-shock association during the CPFE may cause this transition to emerge later in ontogeny. Future experiments will assess these possibilities.

Rosas JM, Alcalá JA, Ogallar PM, Gonzalez G, Gámez AM, Callejas-Aguilera JE *Associative interference facilitates subsequent new learning*

The effect of associative interference upon context processing and context dependence of the information has been well documented

in the literature. Interference treatments such as extinction or discrimination reversal seem to lead to context-specificity of retrieval of both, the interfering information, and the new information learned after the interference treatment has taken place. Recent reports suggest that the effect of interference upon context-specificity of new learning, even when the new information is learned outside of the context where interference took place. On explaining these results, traditional views suggest that the effect of the associative interference on attention is specifically attuned to the context. Alternatively, interference treatments may produce an unspecific increase on attention that might lead to a general improvement in subsequent learning, regardless of whether this new learning involve contexts or not. The results of several experimental series recently conducted in our laboratory exploring this latter idea are presented. Associative interference treatments seem to facilitate temporal conditioning of magazine training and spatial learning in a water-maze in rats, as much as facilitate learning of complex discriminations, and attenuate pre-exposure effects in human predictive learning. Implications for the understanding of the role of interference in context processing and general learning are discussed. The Research presented here was financially supported by Grant PSI2014-52263-C2-1-P from the Spanish Ministry of Economy, Industry and Competitiveness

Russo AS, Parsons RG *Activity of the Mitogen-Activated Protein Kinase in the amygdala and prefrontal cortex associated with individual variation of fear extinction in rats*

Although most people are exposed to a traumatic event at some point throughout the lifetime, only a small portion of people develop post-traumatic stress disorder (PTSD). This indicates the presence of factors which determine those individuals who recover following trauma from those who develop the disorder. Non-human animal studies of Pavlovian fear conditioning have great potential to lead to a better understanding of the neural and behavioral processes that underlie PTSD, and while laboratory studies of fear learning have been very useful, an overwhelming majority of them have not taken into account

variability in fear responses across individuals following fear learning. Here we report that adult, male, Sprague-Dawley rats show significant individual variation in both within-session extinction learning and retention of extinction learning following exposure to a Pavlovian fear conditioning procedure. In these rats, we examined the activation of the mitogen-activated protein kinase (MAPK) expression in the amygdala, medial prefrontal cortex (mPFC), and hippocampus, three areas known to be important for the acquisition and retention of extinction learning. In Experiment 1, rats were euthanized following an extinction training session, and in Experiment 2, rats were euthanized following an extinction retention test session. In Experiment 1, we observed that rats which showed the largest decrease in fear responding over the course of an extinction training session showed higher expression of MAPK in the mPFC, while rats whose freezing levels changed very little over the course of extinction showed MAPK levels equivalent to controls which did not undergo associative learning. We observed a similar pattern in rats which were sacrificed following extinction retention, with rats exhibiting good retention of extinction showing higher levels of MAPK activity in the mPFC compared to rats with poor retention, who did not differ from controls. In these same animals, MAPK expression in the amygdala in rats with particularly good or poor extinction retention did not differ from controls, however rats which showed intermediate levels of retention had increased MAPK activity. In conclusion, we have identified differences among extinction phenotypes in brain areas known to mediate extinction learning. Our data suggest that plasticity in brain areas normally involved in extinction learning is dysregulated in animals which show poor extinction learning.

Saksida LM *Assessing Attention in Rodent Models of Alzheimer's Disease and Schizophrenia*

Neurological and psychiatric disorders such as schizophrenia, attention deficit hyperactivity disorder and Alzheimer's disease have profiles of cognitive impairment that are critical targets for therapeutic remediation. Central to these profiles are deficits in executive func-

tion including impairments in attentional and inhibitory control, sustained goal-directed action and regulation of processing speed. An essential step toward devising treatments to improve these cognitive symptoms is the development of precise behavioural assays that are sensitive both to impairments in preclinical models and to clinically relevant treatments. In this talk I will discuss our touchscreen-based approach toward this goal, which has the potential to achieve more accurate, efficient, and reproducible phenotyping of rodents, and help bridge the translational divide between animal and human studies of cognition. I will focus on tasks that tap into various aspects of attention, including a new rodent version of the continuous performance test, in the context of AD and schizophrenia.

Sangha S *Neural circuits of inhibiting conditioned fear by a safety cue in a fear-safety-reward cue discrimination task*
Clinical disorders arising from maladaptive emotion regulation present a large burden on society worldwide. Many of these disorders show comorbidity, for example, addiction with anxiety disorders. Cues predicting something aversive elicit avoidance and fear behaviors whereas cues predicting reward elicit approach and reward-seeking behaviors. Cues signifying safety have the power to modulate fear and reward-seeking behaviors by informing the organism whether or not the environment is safe. Thus, safety, fear and reward behaviors, and the circuitries governing these behaviors, are intertwined. The majority of studies on reward and fear processing have been conducted in parallel, investigating the circuitries separately in primarily male subjects. If we hope to understand and treat comorbid disorders resulting from maladaptive emotion regulation increased efforts in investigating how these circuitries integrate their functions to influence behavior is needed in both male and female subjects. We have established in male rats that the amygdalocortical circuit contributes to safety-fear-reward cue discrimination. And, our results comparing males and females show that female rats do not suppress conditioned fear in the presence of the safety cue, indicating a failure to regulate fear in 'safe' conditions, and they are more reward responsive during the reward

cue compared to males. Since women are more than twice as likely as men to develop emotion dysregulation disorders, this paradigm offers a great opportunity to tease apart the sex differences in neural circuitry that are generating the behavioral sex differences.

Sangiamo DT, Warren MR, Neunuebel JP *Social context-dependent ultrasonic vocal signaling in mice*
Acoustic signaling is observed throughout the animal kingdom, and in many species, including mice, communication plays a vital role in shaping social dynamics. Mice are highly interactive creatures with diverse behavioral repertoires that are accompanied by an assortment of ultrasonic vocalizations; however, it is unknown if mouse vocal expression depends on social context. Using a novel system to track the vocal behavior of individual mice during automatically identified innate social behaviors and an algorithm developed to group phonically similar vocalizations, we discovered that vocal signals were emitted at different proportions depending on their type and social context. Specific types of vocal signals were emitted at a proportion that was above chance by mice acting aggressively towards another mouse, whereas other types of vocal signals were emitted at a proportion above chance by mice avoiding other animals. Vocal signal types that were emitted above chance in one context were often emitted below chance in other contexts. Lastly, we directly showed that vocal expression impacts the behavior of the social partner receiving these auditory signals. During chases, both males and females slowed down when the mouse chasing them emitted a type of vocal signal that occurred above chance within a chase. In conclusion, our results revealed that ultrasonic vocal signaling in mice is dependent upon specific social actions and these communication signals modulate behavior.

Sevenster D, Haesen K, Vervliet B, Kindt M, D'Hooge R *Prevention and treatment strategies for enhanced contextual generalization*
At the core of anxiety disorders lies the tendency to generalize fear from a threatening to a safe situation. A deeper understanding of

the mechanisms that facilitate and restrain generalization in humans is therefore needed. Rodent studies showed that pre-exposure to a context that is similar to the conditioning context enhanced generalization to that similar context. Due to overlap in features between the contexts, the pre-exposure representation was recalled during conditioning and the shock also became linked to the recalled context representation, resulting in enhanced fear generalization (Rudy & O'Reilly 1999). We investigated, first, whether enhanced generalization as a result of pre-exposure similarly occurs in humans (Experiment 1). Second, we aimed to investigate whether enhanced generalization could be prevented (Experiment 2). An abundance of experimental research demonstrated that pre-exposure to two similar stimuli increases the ability to distinguish between these stimuli. Hence, pre-exposure to not one but two similar contexts should stimulate the ability to distinguish between contexts. Then, presentation of the conditioning context should no longer result in recall of the pre-exposure context. Instead, participants should be able to discriminate between the conditioning context and the similar pre-exposure context. We conducted two experiments, in which pre-exposure took place on day 1, followed by context conditioning on day 2, and ended with generalization test on day 3. Both studies were conducted in healthy human participants. In Experiment 1 we replicated the original animal findings (Rudy & O'Reilly, 1999) in humans and showed that pre-exposure to a context that is similar (but not the same or different) to the conditioning context enhanced generalization of US-expectancy to that context. In Experiment 2, enhanced generalization of US-expectancy was prevented by pre-exposure to two similar contexts. Pre-exposure did not affect generalization of skin conductance response or fear potentiated startle. Finally, post-hoc analyses revealed that enhanced generalization of US-expectancy, if not prevented, could be reduced by a reminder of the conditioning context. These findings demonstrated that generalization could be enhanced and reduced and will guide new therapeutic strategies aiming to reduce fear generalization.

Shang A, Bylipudi S, Bieszczad KM *A role for HDAC3 in the specificity of memory consolidation*

Epigenetic mechanisms like histone acetylation are now known to regulate long-term memory formation in multiple systems of the adult brain, including the sensory cortex. An open question is the nature of epigenetic effects on memory encoding, consolidation and storage. Recent work in the auditory cortex has shown that rats treated with a pharmacological histone deacetylase 3 (HDAC3)-inhibitor (HDAC3i) during consolidation of an auditory associative task have enhanced memory for the behaviorally-salient sound-frequencies in a memory test after training, as well as expanded cortical representation in primary auditory cortex (A1) for the signal-frequencies (Bieszczad et al., 2015). Interestingly, post-training administration of HDAC3i while animals learned to associate a sound with reward over daily sessions of instrumental conditioning had no effect on performance per se. All animals acquired and performed the task identically over 2 weeks of training. Only in a behavioral memory test conducted at the end of training were differences revealed in sound-frequency generalization of the sound-reward association: Rats treated with HDAC3i had a striking peak in the frequency-specificity of the associative memory formed at the sound-frequency of the CS, relative to animals treated with vehicle, whose gradients were flat. Thus, these findings suggest that one role of epigenetic mechanisms for memory is to alter the sensory precision of information consolidated into long-term memory. If so, then performance effects would be revealed in tasks that require sensory discriminations, and stimulus specificity would be evident in both excitatory and inhibitory associations. Here, we used an auditory associative learning paradigm to test the emerging hypothesis that HDAC3 controls the sensory-specificity of long-term memory (Phan & Bieszczad, 2016). Rats (adult male Sprague-Dawley) were trained on a two-tone frequency discrimination (2TD) task and were given immediate post-training injections of either an HDAC3i (RGFP966; 10mg/kg) or vehicle for 3 consecutive days. Only bar-press (BP) responses made duing presentations of the CS+ (5.0 kHz) result in a

water reward; BPs made to the CS- (11.5 kHz) result in an error signal (flashing light) and an extension of the time until the next trial. We found that HDAC3i-treated animals (n=12) learned the 2TD task faster, reaching performance criterion (defined as 2 consecutive days of performance >90% or 3 consecutive days of asymptotic performance, c.v. <0.1) up to two days before veh-treated animals (n=12). Thereafter, all animals reached similar levels of asymptotic performance. Animals then underwent a stimulus generalization test (SGT) to determine memory specificity for the CS+ and CS- sound frequencies. Under extinction conditions, animals were presented with 10 different tone frequencies, including the CS+ and CS-. The number and latency of bar-presses to each test tone were used to construct frequency generalization gradients. HDAC3i-treated animals exhibited more specific memory for the learned frequencies on the SGT, revealed both by a peak in bar-presses at the 5.0 kHz (CS+) sound and a nadir at the 11.5 kHz (CS-) compared to vehicle. Together, this provides behavioral evidence that HDAC3i treatment early in training facilitates incremental learning of sound-specific information, and produces lasting effects on memory specificity. Furthermore, these findings provide support for an epigenetic role to facilitate the “capture” of sensory information from experience into memory.

Sharp JL, Miller-Cahill ME, Fountain SB, Riccio DC *Serial Pattern Retention in Male and Female Rats*

This experiment examined serial pattern retention in rats. Adult male and female rats were trained in a serial multiple choice (SMC) task to perform a pattern of nosepoke responses in receptacles mounted on the 8 walls of an octagonal chamber. Rats learned to nosepoke the pattern, 123-234-345-456-567-678-781-818, where digits represent the clockwise position of successive correct receptacles and dashes indicate brief pauses that served as "phrasing cues." The pattern consisted of three element types: chunk-boundary elements (the first element of each chunk), within-chunk elements, and a terminal violation element "8" that was inconsistent with pattern structure. Rats were trained to a high criterion on the violation elementâĂŤthe most difficult

element to learnâĂŤand were later tested for retention after 24-hour, 2-week, and 4-week retention intervals. Retention for within-chunk elements was significantly better than for chunk-boundary and the violation element after 24-hour and 4-week retention intervals. Retention for chunk-boundaries was significantly better than violation element retention after 2-week and 4-week retention intervals. No sex differences were observed. Because prior behavior analysis and neuropharmacology studies indicate that rats encode different element types via different cognitive mechanisms concurrently, the current study suggests that forgetting of information learned via different cognitive mechanisms may be forgotten at different rates. However, more carefully controlled studies equating training by element type are sorely needed to support such a conclusion.

Sharpe MJ, Mueller LE, Batchelor HM, Schoenbaum G. *Lateral Hypothalamic GABAergic neurons actively oppose learning about the general structure of our environment in favor of cues most proximal to reward.*

We have recently shown that GABAergic neurons in the lateral hypothalamus (LH) are necessary for learning to predict rewards. Specifically, optical inhibition of LH GABA neurons during a cue (and not during reward) in Pavlovian conditioning disrupted both the acquisition and expression of cue-reward associations. This challenges traditional theories of LH function that argue that LH is solely a feeding center- an “output nucleus” for driving appetitive behavior. In the current experiments, we assessed whether LH GABA neurons might also be involved in learning to associate neutral stimuli. For this, we used the sensory preconditioning procedure. Sensory preconditioning involves first pairing two neutral cues together in close succession, so that an association forms between them. This association is then revealed by pairing the second cue with reward, which causes an appetitive response to emerge to both. We found that optical inhibition of LH GABA neurons during the pairing of the two neutral cues enhanced the subsequent ability of the cue not paired with reward to drive appetitive responding. This surprising result can be explained if

LH GABA neurons usually oppose learning about neutral stimuli in favor of learning about cues directly paired with reward. To confirm this, we then assessed whether LH GABA inhibition would disrupt latent inhibition, an iconic task based on the downregulation of processing of neutral cues. Here, we optically inhibited LH GABA neurons during cue presentation in the pre-exposure, when a cue is repeatedly presented alone. Normally this pre-exposure retards subsequent learning when this cue is paired with reward. We found that rats without LH GABA function during pre-exposure subsequently learnt to associate the pre-exposed cue and a novel cue with reward at the same high rate, demonstrating the importance of LH GABA cells in disregarding cues that are not predictive of reward. Taken together with our previous data, these experiments illustrate the importance of LH GABA neurons in resolving the tension between learning about the general associative structure of our world and devoting cognitive resources to cues which are proximal to reward. Such data may make sense of research demonstrating LH dysfunction in schizophrenia- potentially underlying the formation of spurious associations known to contribute to the positive symptoms of the disorder. National Health and Medical Research Council (Australia) overseas biomedical fellowship

Shipman ML, Trask S, Bouton ME, Green JT *Inactivation of prelimbic and infralimbic cortex respectively affect expression of minimally-trained and extensively-trained goal-directed actions*

Several studies have examined a role for the prelimbic cortex (PL) and infralimbic cortex (IL) in free operant behavior. A typical result is that PL lesions render a goal-oriented response habitual (i.e., insensitive to reinforcer devaluation), but leave an extensively trained habit intact. The opposite effect is seen with IL lesions; habitual responding is affected while goal-directed responding is not. To further examine the involvement of these regions in the expression of goal directed and habitual behavior, we trained two different operant responses within-subjects. One response was trained extensively and one was trained minimally. In Experiment 1, rats were implanted with bilateral guide cannulae into their PL. Following recovery, rats per-

formed two responses to produce a food reinforcer, R1 and R2, each in its own context. R1 received extensive training and R2 received minimal training. Rats then received lithium chloride injections either paired or unpaired with sucrose pellets in both contexts until paired rats rejected all pellets. On test day, rats received either an infusion of saline or baclofen/muscimol into the PL and were tested (in extinction) on both their R1 and R2 responses. No habit was demonstrated on either the extensively or minimally trained response, but rats with an inactivated PL showed a selective decrement in responding on the minimally trained response. This suggests a role for the PL in expression of response-outcome associations early in learning. Because of the role of the IL in habits, we then hypothesized that the IL would play a role in expression of an extensively trained response. For Experiment 2, we utilized the same design as Experiment 1 but with IL inactivation at test. We found that extensively trained responding was again sensitive to reward devaluation, but that IL inactivation suppressed the extensively-trained and not the minimally-trained response. The overall pattern of results suggests a double dissociation whereby the PL is involved in expression of minimally trained goal-directed behavior while the IL is involved in expression of extensively trained goal-directed behavior.

Shors TJ *Sexual Violence, Stressful Memories, and Learning to Recover*

One in three women experience sexual violence or trauma in their lifetime, most of them as adolescents and young adults. (World Health Organization, 2013; Shors and Millon, 2016), and as many as one in five students during their college years (Cantor et al., 2015). In a recent study, Shors and colleagues observed that young women with a history of sexual violence report significantly more symptoms of depression, anxiety about the future, and ruminations about the past, all of which were highly correlated with one another (Millon, Chang and Shors, under review). The women reported especially vivid memories of their most stressful life event (presumably the violent encounter), especially its spatial context. They also considered the memory a

significant part of their life story, more so than women reflecting on a stressful event that did not include sexual violence.

The nonhuman female brain is likewise sensitive to these types of stressful life experiences; animal models suggest that aggressive interactions between a pubescent female rodent and a sexually-experienced adult male rodent is stressful and can disrupt processes of learning, including learning to care for offspring. As a consequence, fewer new neurons survived in the hippocampal formation (Shors et al., 2016). Thus, sexual aggression can disrupt learning in animal models, which can thereby reduce neurogenesis through a reduction in cell survival.

Memories for traumatic life events are obviously generated by the brain but often felt in the body. MAP Training is a novel clinical intervention that combines mental training of the brain with physical training of the body (see MAPTRAINMYBRAIN.com). Each session consists of 30 minutes of mental training with silent meditation followed immediately with 30 minutes of aerobic exercise at a moderate intensity. Eight weeks of training significantly reduced symptoms of depression, anxiety, and rumination while enhancing synchronized brain activity and autonomic balance in participants with and without trauma history (Shors et al., 2014; Alderman et al., 2016; Shors et al., 2017). Preliminary data suggest that MAP Training can reduce rumination and the vividness of stressful memories in women with sexual violence history, presumably making these events a less significant part of life stories going forward. We propose that MAP Training is effective because it enhances extinction processes related to the rumination of traumatic/stressful memories during meditation while reducing the associated autonomic nervous system response after aerobic exercise. [Supported by the Brain & Behavior Research Foundation (NARSAD) and The Brain Health Institute at Rutgers University]

Spiegler KM, Smith IM, Fortress AM, Pang KCH *Persistent avoidance in anxiety-vulnerable Wistar-Kyoto rats: The role of danger and safety signals*

Avoidance behavior is a core symptom of all anxiety disorders and post-traumatic stress disorder (PTSD). Environmental cues can drive

avoidance behavior by allowing the individual to predict the onset of an aversive event. Cues that occur at the onset or during an aversive event become danger signals, while cues that occur at the offset or in the absence of an aversive event become safety signals. The Wistar-Kyoto (WKY) rat is used as a model for anxiety-vulnerability. Recently, our lab has shown that WKY rats are differentially reinforced by danger and safety signals compared to Sprague Dawley (SD) rats when avoiding foot shock. Given this finding, the question remained as to whether or not these strains were differentially reinforced by danger and safety signals in pathological avoidance, as measured through extinction (shock removed). WKY and SD rats were trained to avoid foot shock by lever pressing in response to a tone signaling danger. Upon lever pressing, the tone turned off and a flashing light turned on signaling safety. Following asymptotic acquisition of avoidance, extinction learning occurred in one of four conditions: 1) with both danger and safety signals present, 2) with danger signal only, 3) with safety signal only, and 4) with no signals. When both signals were present during extinction, both strains displayed persistent avoidance. However, when only danger signal was present, SD rats extinguished to a greater extent than WKY rats. Likewise, when only safety signal was present, SD rats extinguished to a greater extent than WKY rats. Interestingly, the extinction of individual danger and safety signals in WKY rats appear to be additive, with more weight toward the danger signal. Both strains quickly reduced avoidance responding when neither signal was present. These data suggest that danger and safety signals can individually cause persistent avoidance in anxiety-vulnerable individuals. Such findings have important implications for behavioral treatments of anxiety disorders and PTSD. Biomedical Laboratory Research & Development Service of the Department of Veterans Affairs Office of Research & Development (grant I01BX000132)

Starosta S, Frey M, Kepecs A *Behavioral algorithms and neural substrates of stay-or-leave decisions*

In our daily life we are continuously confronted with decisions about

whether to stay engaged in our current behavior or switch to a new course of action. These stay-or-leave decisions have been mostly studied in behavioral ecology as foraging decisions but little is known about their neural basis. Therefore, we set out to develop a behavioral task inspired by a classic foraging theory from neuroethology to study the neuronal basis of stay-or-leave decisions. The starting point for our studies is a rigorous theoretical framework for foraging decisions describing optimal choice strategies, called Marginal Value Theorem (MVT, Charnov, 1976). MVT describes how to act when foraging in an environment with depleting resources located in discrete patches. Previous studies mostly focused on describing behavioral choices on average and not individual decisions that would allow linking neural activity to moment-to-moment control of behavior. Therefore we designed a behavioral task that enabled us to infer the trial-to-trial choice strategy in a foraging behavior. Mice were allowed to run back and forth between two reward ports that provided water upon entry. With each re-entry into the same port the amount of water decreased while switching to the other port reset water to the full amount. Additionally, we manipulated the effort cost of switching by introducing a variable height bridge in the middle of the track between the ports. In a series of experiment, we showed that the behavior of mice in this task follows the predictions of MVT: increasing the average reward rate or increasing harvest time led animals to leave a port earlier while increasing the effort cost induced longer stays. Surprisingly, when we introduced unexpectedly larger rewards, animals left earlier, in apparent violation of Thornike's law of effect. Although counterintuitive, this choice pattern is predicted by a trial-to-trial updating MVT algorithm. This could be explained by surprisingly large rewards inducing updates to the average expected rate of the environment (MVT) and not to the expected value of the reward ports (classic reinforcement learning). Next, we sought to elucidate the neuronal basis of this foraging behavior. We focused on the dopamine system because of its key role in reward-guided behaviors. We manipulated the dopamine system by antagonizing adenosine A2A receptors that are co-localized and interact with dopamine D2 receptors, enabling

selective targeting of the indirect striatal pathway. We systemically administered the A2A antagonist preladenant while animals were performing the foraging task. This manipulation did not change either effort-dependent choices or the average reward amount when mice left each port. Rather we found that mice continued to poke into a port after it was completely depleted and not yielding water, resulting in oversampling behavior. This led to suboptimal foraging, 30% lower reward per session. In summary we found that mouse foraging follows an optimal choice strategy, described by the choice-by-choice MVT decision rule that runs counter to classic reinforcement learning algorithms. We also showed that foraging decisions are disrupted by pharmacological manipulations of the striatal indirect pathway, suggesting that the basal ganglia are involved in stay-or-leave decisions

Steele CC, Davis IR, Kirkpatrick K *The effect of dietary exposure on impulsive choice in male and female rats: An investigation of individual differences*

The relationship between obesity and impulsive choice has received growing attention over the past decade, but the direction of this relationship is unclear. Recent research in rats suggests that diets high in fat and sugar induce impulsive choice behavior, possibly explaining the relationship between obesity and impulsive choice. However, the role of trait impulsivity in diet-induced impulsivity is not understood. The current study sought to investigate how individual differences in impulsive choice interacted with dietary exposure. Male and female rats completed a baseline impulsive choice task where rats chose between a smaller-sooner reward (1 pellet after 10 s) and a larger-later reward (2 pellets after 30 s). Following the baseline measurement, rats received either a control diet or a high-fat/high-sugar diet for 6 weeks. The rats in both groups were given the same number of calories, so that only the composition of the diet differed between groups. Following the dietary exposure, rats completed an impulsive choice task while maintained on the diet, where the delay to the smaller-sooner reward was manipulated across phases. This study demonstrates how pre-existing individual differences in impulsive choice can

affect susceptibility to the dietary effects on subsequent impulsive choices.

Steinfeld MR, Thrailkill EA, Bouton ME *Extinction of procurement prevents renewal of consumption when an extinguished consumption response is returned to a heterogeneous chain*
Common and sometimes problematic behaviors such as overeating and drug use often consist of a chain of linked instrumental behaviors. Behavior chains minimally consist of a procurement response (R1) and a consumption response (R2), which must be completed in order to gain access to the reinforcer. Research has revealed that a consumption response that is extinguished outside of its chain is subject to renewal when it is returned to the chain (i.e., when it is preceded by the associated procurement response). Two experiments investigated whether the extinction of the procurement response can weaken or prevent the renewal of consumption from occurring. In the acquisition phase, rats learned a discriminated heterogeneous chain of the form S1–>R1–>S2–>R2–>food pellet, where R1 and R2 were distinct lever-press and chain-pull responses (counterbalanced). During the extinction phase, all rats received S2–>R2 extinction trials. During the Experiment 1 test, S2–>R2 was renewed when it was tested as part of the chain (i.e., after S1–>R1). That renewal was abolished, however, if R1 had also been extinguished (with separate S1–>R1 extinction trials). In Experiment 2, we replicated that finding, and also found reduced S2–>R2 renewal in a group that received yoked S1 extinction trials (without being able to perform R1) during the extinction phase. Together, the results represent a potentially novel approach to preventing relapse in the context of a discriminated heterogeneous chain.

Takahashi YK, Batchelor HM, Liu B, Khanna A, Morales M, Schoenbaum G *Dopamine neurons respond to errors in the prediction of sensory features of expected rewards*
Midbrain dopamine neurons have been proposed to signal prediction errors as defined in model-free reinforcement learning algorithms.

While these algorithms have been extremely powerful in interpreting dopamine activity, these models do not register any error unless there is a difference between the value of what is predicted and what is received. Yet learning often occurs in response to changes in the unique features that characterize what is received, sometimes with no change in its value at all. Here, we show that classic error-signaling dopamine neurons also respond to changes value-neutral sensory features of an expected reward. This suggests that dopamine neurons have access to a wider variety of information than contemplated by the models currently used to interpret their activity and that, while their firing may conform to predictions of these models in some cases, they are not restricted to signaling errors in the prediction of value. NIDA-IRP

Thrailkill EA, Trask S, Bouton ME *Can discriminated operants become habits?*
Habits seem common in everyday life; for example, people may habitually eat popcorn when watching a movie in a theater. In this example, as in most others, the habitual behavior is under stimulus control (one is less likely to eat popcorn when not watching a movie), and is thus a discriminated operant. Interestingly, although there is much contemporary research on instrumental habits and actions, no one has demonstrated that discriminated operants (as opposed to nondiscriminated, free operants) can become habitual. We therefore investigated the question using a reinforcer devaluation method. In that method, after operant training, a rat receives separate aversion conditioning with the reinforcer until the reinforcer is rejected. A test of the instrumental response in extinction then reveals whether the behavior reflects the new undesired status of the reinforcer. Rats learned to press a lever for food reinforcers in the presence of a discriminative stimulus (a tone; S). Presses earned reinforcers according to a random interval 30 s schedule in the S. No reinforcers were delivered when S was absent. In Experiment 1, rats received discriminated operant training with presentations of a 30-s S separated by a variable 90-s intertrial interval. Although the amount of training was extensive

(> 1,000 reinforced responses), rats with an aversion to the pellets still reduced their responding in the S. The response thus remained a goal-directed action despite its extensive training. In Experiment 2, rats received an identical amount of response-reinforcer training with the exception that the duration of the S was extended to 8 min instead of 30 s. Here, rats with an aversion to the food pellets responded the same amount in the S as rats without the aversion during the nonreinforced test. Thus, when trained with a longer discriminative stimulus, the response became a habit. The results suggest that sensitivity to devaluation in discriminated operant procedures depends of the duration of the S during conditioning. Implications and possible explanations will be discussed. DA 033123

Trask, S, Keim, CL, Bouton, ME *Factors that Encourage Generalization from Extinction to Test Reduce Resurgence of an Extinguished Operant Response*

In resurgence, an extinguished operant behavior returns when alternative reinforcement for a second behavior is removed. Two experiments tested the hypothesis that increasing generalization from R1 extinction to the test would reduce resurgence. In a first experiment, rats were trained to perform an R1 response. Then, in a second phase, R1 was extinguished while R2 was now reinforced. In the subsequent resurgence test, R1 and R2 were both extinguished. For half the rats, Phase-2 sessions in which R2 was reinforced alternated with sessions in which R2 was not reinforced. Further, half of these rats experienced this for an extended period (25 sessions) and the other for a shorter period (5 sessions). Controls had the same number of Phase 2 sessions, but R2 was never nonreinforced. We hypothesized that experience with nonreinforcement of R2 during R1 extinction would result in improved transfer of R1's inhibition to the resurgence test, and that more experience with these periods would enhance this effect. Consistent with the hypothesis, while both alternating groups showed reduced resurgence, this effect was more pronounced in the 25-session group. Additionally, the magnitude of the resurgence effect in periods of nonreinforcement decreased across

the Phase 2 treatment in the alternating groups. In a second experiment, rats performed an R1 response for a reinforcing outcome (O1). Then, in a second phase, rats experienced two types of Phase 2 sessions (double alternating; 8 each). In one type, R1 was extinguished and R2 produced a new outcome, O2. In the other, R1 was unavailable (and was therefore not extinguished) and R2 produced a different outcome (O3). Rats were then tested in a within-subject manner under three conditions. In one, R1 and R2 were available and not reinforced; resurgence was expected in this condition. In a second, both responses were available and not reinforced, but O2 pellets were delivered freely. In the third condition, O3 reinforcers were delivered freely. During the test, R1 resurgence was weakened relative to the control condition when O2, but not O3, was delivered during testing. One explanation of this finding is that the O2 reinforcer became associated with extinction of R1 and its presence during the test increased generalization of the response inhibition learned during extinction to the test. Together, the results suggest that methods that encourage generalization between R1 extinction and testing can weaken the resurgence effect. RO1 DA 033123 from NIDA to MEB

Travaglia A, Bisaz R, Steinmetz AB, Miranda JM, Sweet ES, Blitzer RD, Alberini CM *Latent infantile memories and critical period mechanisms*

Episodic memories formed during infancy seem to be forgotten, a phenomenon known as infantile amnesia. Infantile amnesia is conserved throughout evolution, as it has been described in humans as well as in rodents. In spite of this apparent memory loss, early life experiences influence brain development and predispose to psychopathologies, raising the question of which mechanisms underlie infantile memory formation. Using the contextual fear based task inhibitory avoidance (IA) in infant rats, we are studying the molecular and cellular mechanisms by which memories are acquired and stored during the infantile amnesia period. We found that early life experiences are not lost but stored as latent memory traces for a long time: later reminders reinstate a robust and long-lasting memory.

The formation of the latent infantile memory requires the hippocampus and employs mechanisms typical of developmental critical periods, including a BDNF- and mGluR5-dependent expression switch of NMDA receptor subunits from 2B to 2A. Moreover, BDNF administration or mGlur5 activation rescues the infantile amnesia. We then extended our finding to a non-aversive hippocampal-dependent learning paradigm, by employing the object location (OL) task. We suggest that the hippocampus, like sensory systems, undergoes a developmental critical period to become functionally competent. These results may have an important impact on both basic science and clinical treatments of cognitive and neuropsychiatric disorders of developmental origin. R01-MH074736

Twining RC, Herbst MR, Kirry AJ, Lepak K, Durigan D, Gilmartin MR *Selective silencing of ventral hippocampal inputs to the prefrontal cortex during trace fear conditioning impairs contextual memory.*
The acquisition of trace fear conditioning, in which an auditory conditional stimulus (CS) and a shock unconditional stimulus (UCS) are associated across an empty 20-sec trace interval, requires activity in both the prefrontal cortex and hippocampus. These areas are thought to interact to "bridge the gap" to allow learning. We have previously described a bridging signal in the prelimbic (PL) area of the prefrontal cortex, where approximately 30% of the cells exhibit sustained increases in learning-related firing during the trace interval (Gilmartin & McEchron, 2005). Optogenetic silencing of this neuronal activity specifically during the trace interval blocked the formation of a trace fear memory. What remains unknown, however, is which subcortical inputs to the PL are necessary to support trace conditioning, when precisely they are important, and to what extent these inputs control learning-related neuronal spiking. Given the importance of ventral hippocampal (VH) input to the PL during spatial working memory and emotional regulation, we hypothesized that VH input to PL during acquisition is required to support both cued fear learning and the observed bridging signal. Here we optogenetically silenced VH terminals in the PL cortex during each trial of trace fear conditioning

(70 seconds across CS, trace interval, shock) across 3 days (2 trials/day). Fear to the CS and context were tested the following days, prior to each training session. In addition, we recorded single unit activity in a subset of these rats using chronically implanted optrodes. Results indicate that rats without VH input to the PL cortex during training exhibited significantly less freezing and were slower to initiate freezing in the shock-associated context. On the other hand, cued fear memory was intact in all rats. Furthermore, if the VH-PL pathway was silenced during the context fear test session, the contextual fear deficit was reversed. Importantly, there was no effect of silencing the VH-PL pathway at test in rats that were trained with this pathway intact. Taken together, these findings suggest that although the VH and PL are both needed for the formation of cued fear memory in trace conditioning, direct communication between them is not important for the CS-UCS association. Instead, the VH-PL pathway is required to form a fear memory of the context where an emotionally salient event occurred. Intriguingly, plasticity in this pathway at the time of training may be important for the subsequent rapid retrieval of fear memory. Whitehall Foundation Research Grant 2014-08-67. National Science Foundation IOS:1558121

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

Fear conditioning studies in rodents allow us to assess vulnerability factors which might underlie fear-based psychopathology such as post-traumatic stress disorder (PTSD). Despite PTSD being more prevalent in females than males, very few fear conditioning studies in rodents have tested females. Our study assessed fear conditioning and extinction in male and female rats using both fear-potentiated startle and freezing behavior as measures. Rats were trained to fear cues that predicted the occurrence of shock and then subsequently exposed to an extinction training procedure where the cue was presented repeatedly in the absence of shock. Retention of the extinction memory was assessed the next day. Our results showed that females exhibited less retention of fear extinction, but only when measured by

fear-potentiated startle. Our results highlight the importance of using multiple indices of fear behavior, particularly when comparing sexes on measures of extinction learning.

Whitlow JW, Ferris N *On the representation of novelty in associative learning*
Pavlov identified stimulus novelty as an unconditioned stimulus that elicited the "what-is-it" reflex, but little consideration has been given to the role of novelty as a conditioned stimulus. Fundamental to such consideration is understanding the nature of the representation of novelty in associative learning. We propose that novelty is represented in two different ways concurrently. It is represented as a stimulus feature, termed Novelty, that functions much like standard stimulus features such as color, shape, or location. It is also represented as the collection of common elements that are posited in various associative theories to be the elements shared among a collection of nominal stimuli. Implications of this perspective are examined in relation to empirical studies. Supported by the Psychology Graduate Program, Rutgers-Camden

Wiersielis K, Ceretti A, Salvatore M, Lefebo H, Famularo S, Cantoral V, Jang H, Bangasser D *Corticotropin releasing factor in the medial septum impairs spatial learning in rats*
Stress can disrupt a variety of cognitive processes, including learning and memory. Previous studies in rodents have demonstrated that central infusions of the stress-neuropeptide, corticotropin releasing factor (CRF), can disrupt mnemonic processes. However, where CRF is working within the brain to regulate cognition is largely underexplored. A candidate region for direct CRF regulation is the medial septum (MS), because this forebrain cholinergic nucleus is critical for spatial learning and CRF receptors are found on cholinergic neurons therein. Here we assessed whether administering CRF directly into the MS impaired spatial learning in male and female rats. Specifically, we infused different doses of CRF or vehicle into the MS prior to testing on an object location task, which tests spatial learning, and

a novel object recognition task, which does not test spatial learning. On the object location task, we found that CRF in the MS reduced time spent exploring the displaced object compared to the familiar object, suggesting that this manipulation impairs spatial learning. In addition, males were more sensitive to this effect than females, such that a low dose of CRF in the MS that had no effect in females disrupted object location learning in males. In the novel object recognition task, CRF in the MS did not decrease preference for the novel object in either sex, suggesting that the effects of CRF in the MS are specific to spatial learning. Future experiments will examine the influence of circulating ovarian hormones in regulating sensitivity of the MS to CRF. Collectively, these studies reveal that CRF in the MS selectively impairs spatial learning, especially in males, highlighting an unexplored mechanism by which stress can regulate cognition. Clinically, these findings suggest that drugs which block the effects of CRF represent a viable therapeutic option to treat cognitive deficits that characterize certain stress-related psychiatric disorders.

Williams AR, Lattal KM *The Behavioral and Neurobiological Characteristics of Rapid Reacquisition of Conditioned Fear following Extinction*

Several phenomena demonstrate that extinction does not erase the original memory formed during acquisition. The most commonly studied of these include spontaneous recovery, contextual renewal, and reinstatement. Less is known about rapid reacquisition, in which a mild conditioning episode can completely restore the behavior that is eliminated during extinction. The research presented here uses a behavioral model of reconditioning that allows for a direct comparison of contextual fear acquisition and reacquisition. We find that post-extinction reconditioning leads to a rapid reacquisition of contextual fear relative to initial acquisition, suggesting that the animals have not lost the original acquisition memory. Further, we show that this rapid reacquisition of fear is insensitive to the amount of extinction (brief vs. massive) and is specific to the context in which initial contextual fear conditioning occurred. Finally, we explore the neurobiology of rapid

reacquisition via pharmacological and histological approaches. In a pharmacological study, inhibition of the bed nucleus of the stria terminalis with GABA receptor agonists caused a significant reduction of rapid reacquisition. Further, examination of activity markers (cfos and histone 4 lysine 8 acetylation) following reconditioning and conditioning shows differential involvement of cellular mechanism within several regions of the fear circuit. These results suggest that post-extinction reconditioning differs behaviorally and biologically from initial conditioning. These results are significant because rapid reacquisition of fear behavior provides a potential behavioral correlate of post-traumatic stress disorder symptoms, such as exaggerated startle response and hypervigilance. Using this model, researchers can begin to probe the behavior, neurobiology, and potential therapeutic targets of these specific PTSD symptoms.

Wilson WJ *Pavlov's 1923 visit to Battle Creek*
John Harvey Kellogg, chief medical officer of the Battle Creek (MI) Sanitarium, was a fan of Pavlov's work on digestion, and visited Pavlov's lab in 1907. He arranged for Pavlov to visit his sanitarium in 1923, where a former assistant of Pavlov, Wladimir Boldyreff, was conducting research. Kellogg's goal was to promote healthy living through proper diet; a solid understanding of digestion being essential to this goal. Boldyreff had brought Pavlov's breakthrough gastric surgical techniques to the US, and his research at Kellogg's sanitarium was making important contributions to our understanding of digestive processes. Pavlov spent a week at the Sanitarium; he gave his blessing to his name being associated with Boldyreff's institute (thereafter, until Boldyreff resigned, the "Pavlov Physiological Institute of the Battle Creek Sanitarium"), and expressed optimism that important discoveries in conditioning would come from the Institute. This was not to be, as the Institute's main focus remained digestion (Kellogg seemed to care little about the brain). We provide detailed information about Boldyreff, the Institute, and Pavlov's visit. Support from Albion College

Young JW, Light GL *Attentional assessment across species reveal putative mechanisms, biomarkers, and treatments for clinical populations*

There has been a fundamental failure to translate preclinically-supported compounds into novel psychiatric treatments. That failure has been driven by a lack of suitable animal models of disease with concomitant biomarkers of neural-circuit function across species (Young and Geyer, 2015). Electroencephalographic (EEG) biomarkers of behavioral performance are direct assays of neural system functioning with compelling opportunity for cross-species translation (Featherstone et al, 2015). The recently developed 5-choice continuous performance test (5C-CPT) provides an example for integrating behavioral outcomes and neurophysiological biomarkers. Designed to quantify cognitive control (attention) and response inhibition in rodents and humans, the 5C-CPT has demonstrable cross-species validity including; a) 36 hr sleep deprivation-induced deficits; b) amphetamine-induced improvement; c) parietal requirement for performance from human fMRI and rodent lesion studies; and d) vigilance decrement observations across time [see (Cope and Young, 2017)]. Importantly, this task is also clinically sensitive as patients with schizophrenia exhibit deficient performance (Young et al, 2017). Until recently, it was unclear whether attentional deficits in schizophrenia patients corresponded to altered EEG biomarkers. Early evidence suggested attentional deficits in patients with abnormal EEG markers, with the latter also seen in unaffected relatives. This effect was limited however, and focused around sensory event related potentials (ERPs; P1 and N1), perhaps as a result of using the degraded stimulus CPT that places demands on perceptual processing. In contrast to other widely used human continuous performance tasks, the 5C-CPT places less of a burden on perception or other cognitive domains. In schizophrenia patients performing the 5C-CPT, we identified decreased amplitude of N2 and frontal non-target P3 ERPs compared with healthy subjects (Young et al, 2017). We have also observed that poorly performing healthy subjects exhibited: 1) reduced frontal non-target P3 amplitudes; 2) had higher response disinhibition; 3) this deficit was

reversible using the frontally-specific dopamine degradation blocker tolcapone; which 4) reduced the response disinhibition of these subjects (Bhakta et al, Accepted). Hence, the reduced frontal non-target P3 of healthy humans and their response inhibition was remediated with a frontal-specific treatment. Human and animal EEG studies have identified activation decrements in similar regions within the attentional network, concurrent with regions identified via fMRI studies. Studies are currently ongoing to determine whether mice similarly exhibit frontal non-target P3 EEG measures during 5C-CPT performance. Future studies utilizing the 5C-CPT and other novel cross-species behavioral assays [e.g., (Bismark et al, 2017)] aim to bridge the translational gap that limits the development of CNS therapeutics. These new tests also enable cross-species assessment of the contribution of genetic disease models to the attentional and neurophysiological abnormalities observed in neuropsychiatric patients. With greater predictive validity, drugs targeting such cognitive dysfunction are likely to prove more efficacious in psychiatric conditions. Thus, the attentional/EEG work in the 5C-CPT is an example of the ability to bridge the translational pharmacotherapeutic development divide.

Yuan X, Marton T, Shuler MGH *A New Behavioral Framework for Testing Novel Value Variables Enabling Temporal Decision-Making*
We present a behavioral task to test novel value variables that we hypothesize may enable temporal decision-making in animals. Literature describing delay discounting, optimal foraging, and temporal difference reinforcement learning currently provides no systematic or unifying explanation of temporal decision-making. The value variables we normatively derived provide a theoretical unification of delay discounting and optimal foraging. These value variables are distinct from the values variables learned through temporal difference reinforcement learning which, in addition to producing less-optimal temporal decision-making, is also experimentally contradicted. More specifically, we have reimagined how the brain represents sources of rewards. We hypothesize that a key variable represents the intrinsic value of a specific pursuit, independent of the reward rate of

the environment. We have formalized the contrasting observations from delay discounting and optimal foraging as a consequence of their difference in the duration in which a rewarding option remains available: rewarding options in delay discounting are only available instantaneously, whereas those in optimal foraging are available continuously in the task. Delay discounting and giving-up on a foraging patch therefore form extreme ends of a continuum of temporal decision-making problems. In our behavioral design, mice are trained to wait for rewards in a two-port chamber, wherein each port delivers rewards according to the same default reward time distribution. When a cue signals the limited availability of a definite extra reward to be delivered at one specific port —the Sometimes Signaled Extra (SSE) port— the animal can receive the extra reward by remaining longer in the SSE port if it were there already. If the animal is in the other port —the Always Default (AD) port—, the optimal switch time depends on the delay for which the extra reward in the SSE port can be expected to remain available. This behavioral framework bridges delay discounting tasks and optimal foraging tasks and enables validation of our hypotheses: i) the representation of reward value is pursuit-specific; ii) the duration over which a rewarding option is available influences temporal decision-making in a predictable fashion.

Zelikowsky M *Neuropeptidergic control of stress-induced effects on fear and social behavior*

Chronic stress causes severe, detrimental psychological and behavioral effects but its neural basis is poorly understood. We show that prolonged social isolation stress (SIS) in mice alters multiple defensive behavioral responses, including enhanced aggression, persistent freezing to innate and learned fear stimuli, and increased reactivity to noxious stimuli, suggesting a profound change in internal state. This pervasive behavioral influence is accompanied by widespread up-regulation of the Tachykinin2 gene, in multiple brain regions. Pharmacological, neuronal and genetic loss-of-function manipulations revealed dissociable, region-specific requirements for Tac2 signaling in the distinct behavioral effects produced by SIS. Overexpression of

Tac2, in conjunction with activation of Tac2+ neurons, promoted SIS-like behavioral effects in group-housed mice, implying that upregulation of Tac2 is a major contributor to the effects of SIS. These data suggest that the diverse behavioral expressions of an internal state caused by a chronic stressor may be coordinated via a distributed action of a single neuropeptide acting in multiple brain regions.

Zhao L, Wang X *Adaptive Vocal Control by Marmosets in Social Communication*
Humans are known to exhibit great flexibility in vocal control in social context. Non-human primates, however, are believed to be largely inflexible in the production and modification of their species-specific vocalizations, which would limit their ability in carrying out effective vocal communication in complex acoustic environment. In particular, monkeys are thought to be unable to voluntarily modify the spectrotemporal structure of their calls, which in humans is actively controlled during vocal communication. Here we tested the ability of marmoset monkeys (Callithrix jacchus), a highly vocal New World species, to modify their vocal production in the presence of interfering sounds and found that they are able to modify both the overall and specific structures of their vocalizations during ongoing vocal exchanges with conspecifics. When facing interfering sounds of particular spectral contents, marmosets steered their vocalizations away from the spectrum of an interfering sound. They also exhibited the ability to make transient and anticipatory changes in their vocalizations to reduce overlap with interfering sounds. These observations indicate a certain degree of voluntary vocal control and suggest vocal learning in social context by marmosets. Author affiliations: Department of Biomedical Engineering, Johns Hopkins University School of Medicine

Zhou J, Stalnaker T, Ramus S, Schoenbaum G *Orbitofrontal ensembles encode current state or "place" within an odor sequence task*
Orbitofrontal cortex (OFC) has been proposed to encode a cognitive

map of task space. This map is thought to be particularly important when the current state or local position in the map cannot be derived from observable external events alone. However while this idea has been proposed, it has been difficult to dissociate representation of a cognitive map from representation of information about reward and local value. Does the OFC only represent associative information that is relevant to representing outcomes or even just value on a particular trial? Or does it encode associative information or task structure in a way that can be dissociated from the current value? To begin to address these questions, we developed an odor sequence task in which a cognitive map of the "place" in the sequence was both stable throughout the session and could be used to facilitate performance on some specific trials. This allowed us to test whether OFC neurons would allow us to decode information about the current trial and prior or future trials (position in the sequence) and whether any such decoding was independent of value. Rats sampled one of 16 odors on each trial and made a go or no-go response to obtain reward or avoid a prolonged ITI. The 16 odors were organized into four partially-overlapping 6-odor sequences (1a, 1b, 2a, and 2b). The odors in the first 2 positions of each sequence (S1, S2) were unique, like the unique arms of a spatial maze. The odors in the other 4 positions (S3 - S6) were shared across two sequences (1a and 1b, 2a and 2b), like common arms in a maze. In sequences 1a and 1b, the shared odors made identical reward predictions, whereas in sequences 2a and 2b, some made opposing predictions. On trials where the common odor made opposing predictions in the different sequences (2a vs 2b), the rats had to recall past information to make correct choices (analogous to a T maze where choices at the T might depend on prior trials). With sufficient training, rats made correct responses on >75% of all the trial types generally and >90% in many sessions. This included trial types that required them to “look back” several trials to the unique arms of the sequence to make the correct response. This indicates that rats maintained information about their current state or place in the sequence, even when that information was hidden or unobservable from current events. We recorded more than 1000 sin-

gle units in the OFC from these rats (n=7) and performed single-unit analysis and ensemble decoding analysis to investigate how representations of the different states were organized by neural activity in OFC. We found that value was a primary determinant of activity in the OFC throughout a trial. This included both current trial value as well as the value of the current trial for predicting future trials. However in addition to this contribution, we also found a significant amount of information was present about the position of the current trial in the sequence, independent of its meaning with regard to value. These data suggest that OFC represents a model of environmental associative structures that is embedded with but dissociable from biological needs. Funded by ZIA-DA000587 to GS at the NIDA-IRP

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