Pavlovian Society
Annual Meeting, 2019
Coastal Harbour Hotel

October 3–6, 2019
Vancouver BC, Canada

Overview

Thur	6:00–10:00 PM	Opening Reception Coal Harbour A Hors d'Oeuvres & Cash Bar
Fri	7:30–8:25	Breakfast
	8:25–12:10	Morning Sessions
	12:10–1:30	Lunch (Exec Committee Meeting)
	1:30–5:30	Afternoon Sessions
	5:30–7:00	Posters & Cash Bar
Sat	7:30–8:25	Breakfast
	8:25–12:00	Morning Sessions
	12:00–2:00	Lunch (WIL Luncheon)
	2:00–5:30	Afternoon Sessions
	5:30–7:00	Posters & Cash Bar
	7:30–9:00	Banquet

Program

Friday (October 4)

7:30–8:25 **Breakfast**
Coal Harbour B

All talks in Coal Harbour A

8:25–8:30 **Catharine Rankin** (University of British Columbia) Welcome

8:30–9:00 **John Freeman** (University of Iowa) Past President Lecture: Category Learning in Rats

9:00–10:25 **Symposium 1:**

* **Stan Floresco** (*University of British Columbia*) Ventral Striatal Circuits Underlying Different Aspects of Aversively Motivated Behavior

* **Catharine Winstanley** (University of British Columbia)

* **Luke Clark** (*University of British Columbia*) Operant influences in realistic slot machine gambling

* **Jared Young, with Bismark AW, Light GA, Bhakta SG, Swerdlow NR, Greenwood T, Cavanagh J, Brigman JL** (*University of California, San Diego*) The Progressive Ratio Breakpoint Schedule of reinforcement: A translational springboard toward understanding effortful motivation abnormalities in psychiatric disorders.

10:25–10:45 **Coffee Break**

10:45–12:10 **Symposium 2: Adaptive Regulation of Fear (Steve Maren, Chair)**

* **Justin Moscarello** (*Texas A&M*) Fear, Anxiety, and Two-Way Signaled Active Avoidance

* **Susan Sangha** (*Department of Psychological Sciences and Purdue Institute for Integrative Neuroscience, Purdue University, West Lafayette, IN USA*) Adaptive regulation of fear and reward behaviors while learning about safety cues

* **Melissa Sharpe** (*University of California, Los Angeles*) Reward learning shapes the fear circuit

* **Steve Maren** (*Texas A&M University*) Prefrontal-thalamic pathways involved in emotional regulation

12:10–1:30 **Lunch (on your own)**
Executive Committee Meeting (TBD)

1:30–1:50 **Invited Talk**

* **Todd Allen** *(University of Northern Colorado)* A visit to Ivan Pavlov's laboratory in Saint Petersburg, Russia

1:50–3:30 **Symposium 3: Invertebrate Learning (Susan Sangha, Chair)**

* **Kristin Scaplen, with Talay M, Salamon S, Nunez K, Waterman G, Gang S, Song SL, Barnea G, Kaun KR** (*Brown University*) Circuits that encode and express alcohol -associated preference

* **Jackie Rose** (*Behavioral Neuroscience Program, Department of Psychology, Western Washington University*) Classical conditioning of the C. elegans mechanosensory withdrawal response.

* **Gaynor Spencer, with Carpenter S, Rothwell CM, de Hoog E, Walker S.** (*Dept. of Biological Sciences, Brock University, ON. Canada.*) Enhancing and extending memory: why vitamins might like the dark.

* **Amanda Crocker, with Sarikaya K, Pil B, Marriott J, Taber K, Vinton E** (*Middlebury College*) A novel mediator of pain memory in adult Drosophila melanogaster.

3:30–3:50 **Coffee Break**

3:50–4:30 **Invited Talk**

* **Noelle Etoile** (University of California San Francisco) Learning in *C. elegans*

4:30–5:30 **Symposium 4: Human Imaging and Pavlovian Learning (Beck Todd, Chair)**

* **Beck Todd** (University of British Columbia)

* **James Kryklywy, with Anderson AK** (*University of British Columbia; Cornell University*) Neural representations of hedonic touch

* **Vladimir Miskovic** (*Binghamton University*) Aversive Learning in the Human Visual System

5:30–7:00 **Posters and Cash Bar**
Coal Harbour B

Saturday (Oct 5)

7:30–8:25 **Breakfast**
Coal Harbour B

8:25–8:30 **Catharine Rankin** (University of British Columbia) Welcome

8:30–10:00 **Symposium 5: Cortical regulation of motivated behaviour (Mihaela Iordinova, Chair)**

* **Shauna Parkes** (*CNRS, INCIA, Université de Bordeaux*) Cortical contributions to goal-directed behaviour in rats.

* **Geoffrey Schoenbaum** (*NIDA-IRP*) Dopaminergic prediction errors are necessary for updating orbitofrontal representations of expected outcome value and identity

* **Jeremy Seamans** (*UBC*) Conditioning to emotional events by Anterior Cingulate Cortex neurons

* **Mihaela Iordanova, with Esber, Deroche, Schoenbaum** (*Concordia University; Brooklyn College, National Institute on Drug Abuse*) Conditioned Inhibition in the orbitofrontal cortex

10:00–10:40 **Women in Learning Talk**

* **Sheena Josslyn** (University of Toronto)

10:40–11:00 **Coffee Break**

11:00–12:00 **Invited Talks**

* **David Glanzman** (*University of California Los Angeles*) Synaptic plasticity and long-term memory: An uncertain relationship

* **Simon Chen, with Yin XM** (*University of Ottawa*) Dissecting Neural Circuits Underlying Delayed Motor Learning in the 16p11.2 Deletion Mouse Model of Autism

12:00–2:00 **Lunch / Women in Learning satellite meeting**
TAPshack Coal harbour (See map on last page)

2:00–3:30 **Symposium 6: Stress-Enhanced Fear Learning (Michael Fanselow, Chair)**

* **Michael S. Fanselow** (*UCLA*) Advantages of titratable stressors and quantifiable behavioral indicators in revealing the impact of stress.

* **Stephanie Sillivan** (*Temple University; The Scripps Research Institute-Florida*) microRNA regulation of persistent stress-enhanced memory

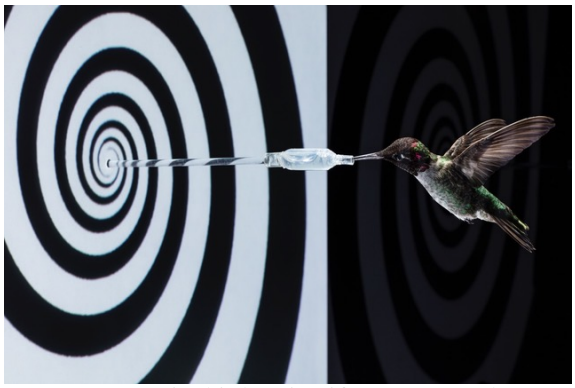
* **Moriel Zelikowsky** (*University of Utah*) Stress-enhanced fear learning and violence

* **Matt Lattal** (*Oregon Health & Science University*) Persistent effects of stress on reward-related behaviors)

3:30–3:50 **Coffee Break**

3:50–5:30 **Invited Talks**

* **Tim Bussey** (*University of Western Ontario*) Translation, open science, and data sharing using touchscreen cognitive assessment)



An Anna's Hummingbird, scientific name: *Calypte anna*, flying in front of an image of a spiral in a lab. This is a reconstruction of an experiment that tests the visual perception of hummingbirds by playing optical illusions, such as looming or receding spirals, in front of them. Research conducted by graduate student Benny Goller. Photographed in the Altshuler lab at the University of British Colombia, Vancouver, Canada. Research contact: Doug Altshuler, professor, email: doug@zoology.ubc.ca, Additional contact: Benny Goller, email: benny.goller@gmail.com. Photo by Anand Varma.

* **Marco Prado, with Beraldo FH, Palmer D, Memar S, Wasserman DI, Franco R, Colleman K, Liang S, Cowan MF, Gee T, Bartha R, Strother SS, Winters BD, Saksida LM, Prado VF, Bussey TJ** (*The University of Western Ontario*) Mousebytes: an open access database and repository for touchscreen-based cognitive data

* **Susanne Schmid, with Scott K, Moehrle D** (*Anatomy & Cell Biology, Schulich School of Medicine & Dentistry, University of Western Ontario*) Cognitive testing in an animal model for autism

* **Ralph Miller, with Li A, Alcaide DM, Witnauer JE, Castiello De Obeso S, Murphy RA** (*SUNY-Binghamton, SUNY-Brockport, University of Oxford*) Contrasting number of trials with duration of trials in contingency learning

5:30–7:30 **Posters and Cash Bar**
Coal Harbour B

7:30–9:00 **Banquet**
Coal Harbour A
Speaker: **Doug Altshuler** (University of British Columbia) Encoding of optic flow in Anna's hummingbirds, zebra finches, and pigeons
Awards

Posters

Generally alphabetical by author except for some moved between days.

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

1. **Agee LA, Hilz E, Lee HJ, & Monfils MH** (*UT Austin*) Disambiguating Arc mRNA expression following long-term memory recall of a socially transmitted food preference and fear association

2. **Ash AM, Chahley E, Seib DR, Snyder JS** (*UBC*) Adult-born neurons inhibit developmentally-born neurons

3. **Asok A, Leroy F, Parro C, De Solis CA, Ford L, Fitzpatrick M, Rayman JB, Kandel ER** (*Columbia University, Howard Hughes Medical Institute*) A temporally-selective gating mechanism for aversive experiences.

4. **Biddle M, Collins B, Knox D** (*University of Delaware*) Estrogen receptor activation and susceptibility to traumatic stress in an animal model of PTSD.

5. **Bolaram, A, Coe, TE, Power, JM, Cheng, DT** (*Auburn University; University of New South Wales*) Differential delay eyeblink conditioning in humans using perceptually similar conditioned stimuli.

6. **Boutros SJ, Krenik DK, Holden S, Unni VK, Raber J** (*Dept. of Behavioral Neuroscience, OHSU; Jungers Center for Neuroscience; Division of Neuroscience, ONPRC*) Effects of common supplementary cancer treatments on learning and memory

7. **Broschard MB, Love BC, Kim J, Freeman JH** (*University of Iowa*) Role of Medial Prefrontal Cortex in Rat Category Learning

8. **Buhusi M, Griffin D, Lee FS, Buhusi CV** (*Psychology, Utah State University; Psychiatry, Weill Cornell Medical College*) BDNF Val66Met Genotype Alters Latent Inhibition of Conditioned Fear

9. **Chalkia A[1], Vanhasbroeck N[1], Zenses A-K[1], Stemerding L[2], Boddez Y[3], Kindt M[2], Van Oudenhove L[1], Beckers T[1]** ([1]*KU Leuven, Leuven, Belgium;* [2]*University of Amsterdam, Amsterdam, The Netherlands;* [3]*University of Groningen, Groningen, The Netherlands*) Directed forgetting of emotional memories

10. **Cole KE, Lee J, Parsons RG** (*Stony Brook University, NY*) Subthreshold fear conditioning produces a rapidly developing neural mechanism that primes subsequent learning

11. **Russo AS, Parsons RG** (*Stony Brook University*) The Effect of Inhibition of the Infralimbic Cortex on Extinction Learning and Recall Using a Fear-Potentiated Startle Paradigm

12. **Colon LM, Poulos AM** (*University at Albany, SUNY*) Role of neonatal and pubertal gonadal hormones in the organization of context fear conditioning..

13. **Cooke MB, O'Leary TP, Harris PK, Brown R, Snyder JS** (*University of British Columbia*) Pathfinder: open source software for analyzing spatial navigation search strategies

14. **Cushman JD, Drew MR, Krasne FB** (*JDC: NIEHS-NIH; MRD:Center for Learning & Memory, Dept Neurosci, UT Austin; FBK: Dept Psychol & Brain Res Inst, UCLA*) The Environmental Sculpting Hypothesis of Postnatal Hippocampal Neurogenesis

15. **Desrochers SS, Nautiyal KM** (*Psych and Brain Sciences, Dartmouth College*) A convergent role of serotonin signaling in conditioned inhibition and instrumental response inhibition

16. **Dowell JR, Datuin E, Escobar M** (*Oakland University*) Amelioration of Spatial Memory Deficits in Rats Receiving Early Prenatal Exposure Alcohol

17. **Dulka BN, Trask S, Helmstetter FJ** (*University of Wisconsin-Milwaukee*) The Effects of Aging on Memory and Activity-Driven Protein Degradation

18. **Dybing K, Faruqi W, Aguilera J, Dahlberg L, Rose J** (*Behavioral Neuroscience Program, Western Washington University, Bellingham, WA*) Long Term Memory for Associative Conditioning and Glutamate Receptor Expression.

19. **Ehlers VL, Yousuf H, Smies CW, Moyer JR** (*University of Wisconsin - Milwaukee*) Ventral hippocampal neuronal excitability and immediate early gene expression following trace fear learning.

20. **Escobedo A, Lee CHL, Sowinski EM, Herakovich R, Sangha S** (*Department of Psychological Sciences, Purdue University & Purdue Institute for Integrative Neuroscience*) Effects of the partial NMDAR agonist D-Cycloserine on the acquisition of discriminative safety learning and consolidation of fear extinction

21. **Conoscenti MA, Fanselow MS** (*Integrated Center for Learning and Memory, Brain Research Institute, Department. of Psychology, UCLA, Los Angeles, CA; The Staglin Center for Brain and Behavioral Health, UCLA, Los Angeles, CA*) Chronicity of stress modulates its behavioral and neurobiological consequences

22. **Gonzalez ST, Marty V, Lele S, Vo R, Yenokian I, Yang CQ, Ahmed K, Spigelman I, Fanselow MS** (*Department of Psychology, University of California, Los Angeles*) Influences of stress severity and sex on changes in fear learning, anxiety and alcohol consumption following stress exposure

23. **Mondello JE, Trott JM, Fanselow MS** (*Department of Psychology, University of California, Los Angeles, CA, USA*) The effects of stress on morphine-induced conditioned place preference

24. **Smith NJ, Trott JM, Fanselow MS** (*UCLA*) Fear, avoidance and punishment: Impact of shock intensity on voluntary vs involuntary processes.

25. **Trott JM, Adison R, Fanselow MS** (*UCLA*) Sex differences in contextual fear learning and generalization.

26. **Hoffman AN, Watson S, Makridis A, Patel A, Giza CC, Fanselow MS** (*Department of Psychology UCLA; Staglin Center for Brain and Behavioral Health at UCLA; Brain Injury Research Center at UCLA; Steve Tisch BrainSPORT Program*) Increased phonophobia and contextual fear in female rats following traumatic brain injury

27. **Farley SJ, Freeman JH** (*The University of Iowa, Iowa Neuroscience Institute*) Optogenetic stimulation of amygdala central nucleus efferent pathways modulate cerebellum-dependent learning

28. **Ferrara NC, Padival M, Loh M, Rosenkranz JA** (*Rosalind Franklin University*) Brief social isolation increases social interaction and cortical drive of basolateral amygdala activity.

29. **Fisher H, Pajser A, Pickens CL** (*Kansas State University*) Prelimbic cortex inactivation during training does not impair later devaluation in a cued-trial multiple-response/multiple-reinforcer operant devaluation task in rats.

30. **Gallo M, Hamid AA, Ofray D, Shleifer D, Hrabarchuk E, Bath KG** (*Brown University*) Effects of early life adversity on motivational vigor and striatal dopamine function in female mice

31. **Gonzalez Magana D, Furtak SC** (*California State University of Sacramento*) Post-conditioning lesions of the perirhinal cortex impairs retrieval of the fear memory to a discontinuous conditioned stimulus.

32. **Gould TJ, Bangasser DA, Holliday ED** (*Penn State and Temple University*) Adolescent stress and nicotine interact to disrupt adult hippocampal-dependent learning and stress response

33. **Haskell AM, Servatius L, Handy JD, Wright WG, Servatius RJ.** (*Syracuse VA Medical Center, Syracuse NY; Department of Psychiatry, Upstate Medical University, Syracuse, NY; Temple University, Philadelphia, PA*) Lifetime Experience of mTBI Blocks Facilitated Acquisition of Eyeblink Conditioning in Anxiety-Prone Veterans

34. **Heroux NA, Horgan CJ, Pinizzotto CC, Rosen JB, Stanton ME** (*Department of Psychological and Brain Sciences, University of Delaware*) Inactivation of the medial prefrontal cortex or ventral hippocampus disrupts incidental context memory and regional immediate early gene expression in adolescent rats

35. **Pinizzotto CC, Heroux NA, Horgan CJ, Stanton ME** (*University of Delaware*) Role of dorsal hippocampal cholinergic activity in context-shock encoding during the Context Preexposure Facilitation Effect (CPFE)

36. **Hilz EN, Monfils, MH, Lee, HJ** (*University of Teas at Austin*) Individual differences in response to amphetamine among female rats.

37. **Debiec J, Chang D-J, Numbers S, Hider J, White A** (*University of Michigan*) The ontogeny of the observational threat learning through scream sounds

38. **Laughlin L, Moloney D, Sears R, Cain C** (*NYU School of Medicine, Nathan Kline Institute*) Reducing shock imminence, but not certainty, greatly improves active avoidance conditioning

39. **Lay BPP, Iordanova MD** (*Center for Studies in Behavioural Neurobiology, Department of Psychology, Concordia University, Montreal, QC, Canada*) Distinct neuronal ensembles within the central nucleus of the amygdala regulate extinction learning.

40. **Gostolupce D, Lay BPP, Iordanova MD** (*Concordia University*) Bidirectional regulation of fear inference in the orbitofrontal cortex

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

1. **Lay BPP, Pitaru A, Boulianne N, Iordanova MD** (*Center for Studies in Behavioural Neurobiology, Department of Psychology, Concordia University, Montreal, QC, Canada*) Distinct neural substrates modulate fear overexpectation and extinction learning.

2. **Lensing A, Boerger R, Zimmerman S, Wu J, Pickens C** (*Kansas State University*) Adolescent/early adult alcohol consumption causes faster omission contingency learning, with the level of consumption correlated with parvalbumin-expressing neurons in the anterior cingulate cortex.

3. **Maes EJP, Sharpe MJ, Gardner MP, Chang C, Schoenbaum G, Iordanova MD** (*Concordia Univ., Montreal, QC, Canada; Psychology, UCLA, Los Angeles, CA; Cell. Neurobio. Res. Br., NIDA IRP, Baltimore, MD*) Causal evidence supporting the proposal that dopamine transients function as a temporal difference prediction error

4. **Markowitz SY, Santos A, Zhang S, Ghemitri N, Fanselow MS** (*Psychology, University of California Los Angeles*) Influences of Variable Stimuli Used in Trauma and Mild Stressor Contexts on Enhanced Fear Response

5. **Marton TM, Hussain Shuler MG** (*Johns Hopkins School of Medicine*) A behavioral paradigm tests if pursuit-based dilating-timestep TDRL explains temporal decision making

6. **McCarthy NA, Peterson RC, Cook-Snyder DR, Miller DP, Servatius RJ** (*Neuroscience, Carthage College, Kenosha, WI; Central New York Research Corporation, Syracuse, NY; Stress and Motivated Behavior Institute, Rutgers Biomedical and Health Sciences, Rutgers, NJ; Psychiatry, State University of New York Upstate Medical University, Syracuse, NY*) Potential role for central amygdala activation associated with avoidance learning in Wistar-Kiyoto rats.

7. **McDiarmid TA[1], Belmadani M[2,3], Liang J, Meili F[1], Mathews EA[4], Mullen GP[4], Rand JB[4,5], Mizumoto K[6], Haas K[1], Pavlidis P[23], Rankin CH[1,7]** ([1] *Djavad Mowafaghian Centre for Brain Health, University of British Columbia, 2211 Wesbrook Mall, Vancouver, British Columbia V6T 2B5, Canada;* [2] *Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, British Columbia V6T 2A1, Canada;* [3] *Michael Smith Laboratories, University of British Columbia, 2185 East Mall, Vancouver, British Columbia V6T 1Z4, Canada;* [4] *Genetic Models of Disease Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma 73104;* [5] *Oklahoma Center for Neuroscience, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104;* [6]*. Department of Zoology, University of British Columbia, 2350 Health Sciences Mall, Vancouver, British Columbia V6T 1Z4, Canada;* [7]*. Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, British Columbia V6T 1Z4, Canada*) Systematic phenomics analysis of Autism-associated genes reveals parallel networks underlying reversible impairments in habituation

8. **Meyer HC, Lee FS** (*Weill Cornell Medicine*) A novel role for the ventral hippocampus in the conditioned inhibition of threat responding

9. **Miller, DP, Miller, JR, Cook-Snyder, DR, Allen, MT, Servatius, RJ, Martino, PF** (*Carthage College, Kenosha, WI; Stress and Motivated Behavior Inst., Syracuse, NY*) Using enhanced CO2 to examine physiological differences in behaviorally inhibited females

10. **Mohammadmirzaei N, Alicea Pauneto A, Knox, D** (*University of Delaware*) The effect of traumatic stress on Mu opioid receptor dynamics in brain regions associated with emotional learning and addiction.

11. **Ng KH, Sangha S** (*Department of Psychological Sciences, Purdue University., Purdue Institute for Integrative Neuroscience*) Learning-related changes in infralimbic cortical activity during conditioned inhibition of fear

12. **Oleksiak CR, Ramanathan KR, Miles OW, Moscarello JM, Maren S** (*Department of Psychological and Brain Sciences and Institute for Neuroscience, Texas A&M University*) Signaled Active Avoidance Performance is Context-Dependent

13. **Opara V, Mahmud A, Cossette M-P, Lay BPP, Iordanova MD** (*Concordia University*) Mesolimbic dopamine regulates aversive prediction error

14. **Adkins JM, Maycon H, Corey J, Jasnow AJ** (*Kent State University*) Stress sex-dependently impairs the ability to acquire and retain safety cues

15. **Ortiz S, Halcomb C, Latsko M, Costanzo C, Beaver J, Dutta S, Adkins J, Jasnow A** (*Kent State University*) Corticosterone administration after early adolescent stress selectively blocks stress-induced potentiation of morphine place preference in adulthood.

16. **Pajser A, Fisher H, Pickens CL** (*Kansas State University*) The role of mu-opioid receptors in conditioned fear learning in high vs. low alcohol drinking rats.

17. **Palmer JL, Eck SR, Ardekani CS, Holley AM, Luz S, Salvatore M, Kim ED, Bhatnagar S, Bangasser DA** (*Temple University, University of Maryland School of Medicine, Children's Hospital of Philadelphia*) Effects of early life adversity on steroid hormones and male sex behavior in rats

18. **Pickens CL, Ma X, Wu J** (*Kansas State University*) The value of inter-trial interval reinforcers is based on absolute, rather than relative, length of the interval during nonreward

19. **Shrestha P[1,‡], Shan Z[1], Marmarcz M[1], Zerihoun AT[1], Chien-Yu J[1], San Agustin Ruiz K[1], Herrero-Vidal PM[1], Pelletier J[2]u, Heintz N[3], Klann E[1,4,‡]** ([1]*Center for Neural Science, New York University, New York, NY 10003;* [2]*Department of Biochemistry, McGill University, Montreal, Quebec;* [3]*Laboratory of Molecular Biology, The Rockefeller University, New York, NY 10065;* [4]*NYU Neuroscience Institute, New York University School of Medicine, New York, NY*) De novo translation in distinct centrolateral amygdala interneurons is required for long-term emotional memories

20. **Pribic MR, Dybing K and Rose JK** (*Western Washington University*) Associative conditioning of a glutamate-dependent locomotor response is modulated by simultaneous activation of GABAergic or cholinergic signaling in C. elegans

21. **Rajbhandari AK, Octeau C, Chavez J, Nguyen L, Keces N, Waschek JA, Khakh B, Fanselow MS** (*Icahn School of Medicine at Mount Sinai*) Optogenetic stimulation of PACAPergic pathway from basomedial amygdala to mICCs increases contextual fear behaviors

22. **Ramsaran AI, Kaushik R, Yeung BA, Gallucci JM, Dityatev A, Josselyn SA, Frankland PW** (*The Hospital for Sick Children, Toronto, ON; University of Toronto, Toronto, ON; Canadian Institute for Advanced Research, Toronto, ON; German Center for Neurodegenerative Diseases, Madgeburg, Germany*) Maturation of hippocampal perineuronal nets underlies the ontogeny of memory specificity

23. **Ray MH, Russ AN, Walker RA, McDannald MA** (*Boston College*) A role for the nucleus accumbens core in adaptive fear scaling

24. **Seemiller LR Gould TJ** (*Department of Biobehavioral Health, Penn State University, University Park, PA*) Ethanol differentially induces fear learning deficits in adolescent and adult male and female C57BL/6J and DBA/2J inbred mice.

25. **Souza RR, Rennaker RL, Hays SA, Kilgard MP, McIntyre CK** (*The University of Texas at Dallas, Richardson-TX.*) Tackling fear memories using vagus nerve stimulation

26. **Totty MT, Warren N, Ramanathan K, Ressler R, Maren S** (*Department of Psychological and Brain Sciences and Institute for Neuroscience, Texas A&M University, College Station, TX 77843-3474*) Neural circuits mediating context-dependent flight behavior in rats

27. **Trask, S, Pullins, SE, Helmstetter, FJ** (*University of Wisconsin-Milwaukee*) Distinct Roles of the Anterior and Posterior Retrosplenial Cortices in Encoding, but not Retrieval, of Trace Fear Memory

28. **Herbst MR, LaViola M, Twining RC, Gilmartin MR** (*Marquette University*) Prefrontal neuronal encoding of threat-related stimuli across the estrous cycle.

29. **Twining RC, Kirry A, Herbst M, Martinez-Cabrera V, Gilmartin MR** (*Marquette University*) Mediodorsal thalamic input to prelimbic cortex is required for trace and context fear memory formation.

30. **Vega-Villar M, Horvitz JC, Nicola SM** (*Psychology Dept., Graduate Center, CUNY, New York, NY; Psychology Dept., City College of New York, CUNY, New York, NY; Dept. of Neuroscience, Albert Einstein College of Medicine, The Bronx, NY*) Experience-dependent changes in the nucleus accumbens underlie acquisition of cued reward-seeking behavior: contribution of NMDARs

31. **Webb EK[1,2], Cutright E[1], Schneider M[1], Mwampashi R[3], Cox C[1], Fast CD[1]** ([1]*APOPO [AntiPersoonsmijnen Ontmijnende Product Ontwikkeling];* [2]*University of Wisconsin-Milwaukee, Milwaukee, Wisconsin;* [3]*Sokoine University of Agriculture, Morogoro, Tanzania*) Training African giant pouched rats as biosensors: New humanitarian applications

32. **Krueger JN, Wilmot JH, Puhger KR, Taratani-Ota Y, Nemes SE, Wiltgen BJ** (*University of California, Davis*) Memory retrieval for context fear is disrupted by widespread increases, but not decreases in hippocampal activity

33. **Puhger KR, Wilmot JH, Wiltgen BW** (*UC Davis*) Post-shock hippocampal activity supports trace fear conditioning - a potential role for replay

34. **Teratani-Ota Y, Lafreniere M, Wiltgen BJ** (*UC Davis*) Segregated object and context processing in CA1

35. **Wilmot JH, Lafreniere MM, Wiltgen BJ** (*University of California, Davis*) Increased c-Fos expression in a TetTag transgenic mouse line.

36. **Wright DW, Bodinayake KK, Kwapis JL** (*Penn State University*) Pharmacological HDAC3 inhibition ameliorates age-related updating impairments in the novel OUL updating paradigm.

37. **Wright KM, Lee E, McDannald MA** (*Boston College*) Roles for dorsal raphe/periaqueductal gray and retrorubral field dopamine in adaptive fear

38. **Yousuf H, Moyer JR** (*University of Wisconsin - Milwaukee*) Intrinsic excitability of retrosplenial cortical neurons varies as a function of sex and age

39. **Yu AJ, Ardiel EL, Rankin CH** (*The University of British Columbia*) Neuropeptides differentially mediate sensitization and dishabituation of distinct response components.

40. **Zhang TR, Guilherme E, Kesici A, Vila-Rodriguez F, Snyder JS** (*University of British Columbia*) Acute neurostimulation effects on hippocampal neurogenesis

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Abstracts

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

Adkins JM, Maycon H, Corey J, Jasnow AJ (*Kent State University*) Stress sex-dependently impairs the ability to acquire and retain safety cues ABSTRACT: Just as learning danger cues is essential for an animal's survival, learning safety cues is critical too. Safety cues can become conditioned inhibitors of fear, in that when they are presented in the presence of the danger cue, they will reduce the fear response that is normally seen when the danger cue is presented alone. It has been shown that people suffering from various anxiety disorders such as post traumatic stress disorder (PTSD) have impairments in discriminating between a danger and safety cue, which in turn, impairs the ability for the safety cue to become a conditioned inhibitor. It is also known that females are more likely to suffer from anxiety disorders such as PTSD than males are, and although research in this realm has been advancing, the reason for this sex difference is currently unknown. Our lab has recently been interested in studying safety learning in male and female mice. The safety learning paradigm consisted of training mice to a danger cue (context) and a safety cue (tone). During the summation test, freezing was measured before the safety cue was presented, and during the safety cue presentation. Our results suggest that male mice can learn the safety cue appropriately—they displayed significantly lower freezing levels during the safety signal sufficiently. However, females continued to display high levels of fear even in the presence of the safety cue, suggesting impaired safety training. Through further investigation we discovered that females require a more extensive safety training protocol in order to successfully learn the safety cue. Next, we aimed to understand the influence of pre and post stress on the acquisition and retention of safety cues, respectively. Results demonstrated that stress prior to or after acquisition, impaired males, but not females, ability to learn and retain safety cues. Together these data suggest that it takes more time for females to learn safety cues, but once it has been acquired, they are resistant to the impairments of stress that is seen in males. Future work will be done to further understand the mechanisms underlying these sex differences in safety learning and the impact of stress on this process.

Agee LA, Hilz E, Lee HJ, Monfils MH (*UT Austin*) Disambiguating Arc mRNA expression following long-term memory recall of a socially transmitted food preference and fear association ABSTRACT: Rats can socially acquire information about their environment through interaction with or observation of a conspecific. In a laboratory setting, one commonly used behavioral model of such social learning is the social transmission of food preference paradigm, in which a rat acquires a preference for a novel food that they have detected on the breath of a conspecific. Rats have also demonstrated the ability to form a fear association with a previously neutral stimuli simply by observing a conspecific react fearfully to

said stimuli. Here, harvested the brains of rats that had socially acquired both a food preference and a fear association following successive recall sessions for each, along with a cage-mate that had directly acquired the fear association and eaten the novel food and a cage-mate that had no experience with either the conditioned stimuli or the novel food. In order to examine the overlap in brain areas recruited for two different forms of social learning, the brains were processed for Arc mRNA expression using catFISH (cellular compartment analysis of temporal activity using fluorescence in situ hybridization (FISH)). Preliminary results indicate that certain prefrontal cortex and hippocampal brain regions may be differentially activated for recall of a socially transmitted food preference and a socially transmitted fear to a cue.

Allen MT (*University of Northern Colorado*) A visit to Ivan Pavlov's laboratory in Saint Petersburg, Russia. ABSTRACT: The International Stress and Behavior Society (ISBS) international meeting is held yearly in Saint Petersburg, Russia. A highlight of attending the ISBS conference is the opportunity to visit Ivan Pavlov's laboratory and office at the Institute of Experimental Medicine (IEM) and have a guided tour. This talk will highlight the experience of taking a step back in time a hundred years to the dawn of classical conditioning. IEM is full of paintings, sculptures, and other tributes to Pavlov. Visiting Pavlov's office and lab at IEM is like opening a time capsule in which his office remains as he left it for the last time in 1936 and still contains personal mementos from his life and career. One of Pavlov's actual dog conditioning chambers is still housed in the Towers of Silence completed in 1926 which minimized noise and vibrations for his conditioning studies. The experimental chamber includes the restraints for the dogs as well as the equipment for the delivery of the food and light stimulus as well as the collection and measurement of saliva. The IEM library contains Pavlov's lab notebooks as well as a personally inscribed copy of his dissertation. The grounds also have a monument to the dogs from a grateful humanity that was commissioned by Pavlov in 1935. Overall, this visit strengthened connections between Pavlovian researchers in the US and Russia. The current head of Pavlovian Institute was impressed with the direct connections between Pavlov, Horsley Gantt who founded the Pavlovian Society, and current researchers who are continuing the integrative physiological work of Pavlov and his students. SUPPORT: University of Northern Colorado Provost Award for Travel

Altshuler D *(University of British Columbia)* Encoding of optic flow in Anna's hummingbirds, zebra finches, and pigeons ABSTRACT: As we move through the world, we perceive the motions of surfaces and objects across our retina, a visual signal known as optic flow. Studies of human behaviour reveal that optic flow is used for controlling virtually all aspects of locomotion such as walking, navigating through cluttered environments, and when driving motor vehicles. Despite the importance of optic flow for everyday activity, there are major gaps in our understanding of how these signals are processed in the brain to allow for coordinated movement. We are investigating how optic flow is used by small birds to guide their flight through different types of environments. We also study how optic flow signals are processed from the midbrain to the cerebellum, in two distinct circuits for locomotion control that are preserved across vertebrates.

Ash AM, Chahley E, Seib DR, Snyder JS (*UBC*) Adult-born neurons inhibit developmentally-born neurons ABSTRACT: Recent reports indicate that lateral inhibition plays a powerful role in selecting which dentate gyrus (DG) neurons are recruited during memory formation. This raises the question of whether developmentally-born and adult-born DG neurons have distinct roles for inhibition, particularly in vivo when neuronal ensembles are selected during memory encoding. To address this we combined chemogenetics and immunohistochemistry for BrdU+Fos to silence and measure activity in developmentally and adult-born neurons as rats learned a spatial water maze task. Specifically, retrovirus was injected into the DG of male rats at 6 weeks of age to express the inhibitory DREADD receptor, HM4Di, in neurons born in adulthood. The same rats were also injected with BrdU to label developmentally or adult-born neurons. At 10 weeks of age rats were injected with either the HM4Di agonist CNO or vehicle, then trained in the water maze (8 trials). We found that silencing a subset of adult-born neurons (aged 4 weeks) increased activity levels in the developmentally-born neuron population. However, silencing adult-born neurons did not affect activation in other adult-born neurons within the DG, suggesting limited interaction amongst the adult-born population. We are currently looking at activation of interneurons (PV+ and SST+) within each treatment group to determine if silencing adult-born cells impacts downstream activity in inhibitory interneurons. Our recent findings implicate PV+ interneurons in the modulatory subcircuit between neuron populations within the DG. SUPPORT: NSERC, CIHR, MSFHR

Asok A, Leroy F, Parro C, De Solis CA, Ford L, Fitzpatrick M, Rayman JB, Kandel ER (*Columbia University, Howard Hughes Medical Institute*) A temporally-selective gating mechanism for aversive experiences. ABSTRACT: Our ability to respond to the sights, smells, and feelings of a life-threatening encounter is critical for survival. How we neurobiologically process and behaviorally defend ourselves against these threats can have a profound influence over our future psychological and behavioral responses. Research in the past decade has provided tremendous insight into how corticolimbic and midbrain circuits control learned and innate defensive behaviors. We have extended upon these studies to discover a novel tri-synaptic pathway between the CA1 subfield of the ventral hippocampus (vCA1), the peri-paraventricular nucleus of the hypothalamus (termed Halo Cells for simplicity), and the periaqueductal gray (PAG). Using a combination of viral, whole-cell patch clamp, chemogenetic, optogenetic, fiber photometric calcium imaging, immunohistochemical, in situ hybridization, RNA sequencing, and network topological approaches, we find that the vCA1→Halo Cell circuit operates through feedforward inhibition to temporally gate the first moments of an unconditioned aversive experience. This gating is apparent irrespective of the mode of sensory input. Our findings provide insight into how a novel hippocampal-hypothalamic circuit alters downstream hypothalamic-midbrain networks to change how the initial moments of an aversive experience are processed.

Marco Prodo, with Beraldo FH, Palmer D, Memar S,

Wasserman DI, Franco R, Colleman K, Liang S, Cowan MF, Gee T, Bartha R, Strother SS, Winters BD, Saksida LM, Prado VF, Bussey TJ, Prado MAM (*The University of Western Ontario*) Mousebytes: an open access database and repository for touchscreen-based cognitive data ABSTRACT: Open Science has changed biomedical research by making research tools and results accessible, shareable contributing to replicability, in order to accelerate and disseminate knowledge. However, this revolution has not yet started in rodent cognitive studies, which are critical for understanding the biological basis of neurodegenerative and psychiatric disorders. Unfortunately, the behavioural techniques used to assess most of cognitive constructs remain woefully unstandardized, limiting comparisons between studies and strains. The growing availability of automated touchscreen-based behavioural tests provides a potential solution, enabling high-throughput approaches for systematic cognitive assessment with easily standardized outputs. Here we present an integration of touchscreen cognitive testing in several mouse models of neurodegenerative diseases, including mutations associated to Alzheimer's disease (AD), Parkinson's disease (PD) and Frontotemporal dementia/Amyotrophic Lateral Sclerosis (FTD/ALS) with an open-access database public repository (mousebytes.ca). This new repository is integrated with automated quality control and enables data storage, data processing, post-experimental interrogation and comparison of mouse cognitive performance. Analysis of hundreds of individual mice suggest that different types of protein misfolding in AD, PD and ALS/FTD mouse models generate specific cognitive deficit signatures. We envision that this new platform will represent significant advances in terms of high-throughput standardized open behavioural assessment and data sharing. Our efforts should enhance data availability, transparency, and comparison of results, allowing crowdsourcing and reuse of mouse cognitive data. Ultimately, the wide accessibility of touchscreen translational cognitive data deposited in MouseBytes will help to increase replicability/reproducibility and aid the translation of findings from bench to bedside. SUPPORT: BrainsCAN, ALS Society Canada, The Weston Brain Institute

Biddle M, Collins B, Knox D (*University of Delaware*) Estrogen receptor activation and susceptibility to traumatic stress in an animal model of PTSD. ABSTRACT: Post-Traumatic Stress Disorder (PTSD) is an anxiety disorder which occurs following exposure to traumatic stress and results in the inability to properly modulate expression of fear memory. Women are twice as likely to suffer from PTSD as men, but this enhanced susceptibility has been difficult to replicate in rodent-based models of PTSD. One reason for this is female rats are resilient to the effects traumatic stress has on persistent fear memory. A possible cause of this is differences in the natural variation of the ovarian hormone estrogen in female humans vs. female rats. In humans, the menstrual cycle typically lasts between 21 and 45 days, with a period of 5-7 days of notably lower levels of estrogen. This can lead to periods where estrogen receptor activation is low in fear circuits, which in turn could represent a window of stress susceptibility in women. In support of this interpretation a number of studies have shown that low estrogen receptor activation leads to either enhanced susceptibility to PTSD or deficits in extinction memory. In rodents, the estrous cycle is typically only 4-5 days, and the period of lower estrogen levels is comparably shorter as well. Thus, there may not be naturally low levels of estrogen receptor activation in female rats. One way to circumvent this potential issue is to pharmacologically antagonize estrogen receptors prior to traumatic stress. By doing this the effects of low estrogen receptor activation on traumatic stress effects in females and males can be examined. To accomplish this goal we used the single prolonged stress (SPS) model of PTSD. SPS consists of serial exposure to restraint forced swim and ether, and approximates core behavioral and neurobiological PTSD symptoms. Prior to conducting SPS or control stress in rats, the estrogen receptor antagonist (ICI182,780; 0.05mg/kg and 0.005mg/kg) was administered subcutaneously to lower estrogen receptor activation prior to SPS. Rats were then subjected to fear conditioning, extinction training, and extinction testing. Rats were then euthanized and key nodes of the fear circuit examined to identify differences in sensitivity to SPS when SPS is conducted under low estrogen receptor activation. While the study is ongoing, preliminary findings suggest that administration of ICI182,780 lowers expression of conditioned fear in stressed and non-stressed rats. The results also suggest that female rats exposed to SPS exhibit deficits in extinction retention. As a control measure, we have also begun to determine the effects of SPS and low estrogen receptor activation on darting behavior; another behavioral measure of fear. The overall results of the study will help determine if low estrogen receptor activation prior to traumatic stress can lead to stress susceptibility and identify key nodes in the fear circuit through which this susceptibility may manifest.

Bismark AW, Light, GA, Bhakta, SG, Swerdlow, NR, Greenwood T, Cavanagh, J, Brigman, JL, Young, JW (*University of California, San Diego*) The Progressive Ratio Breakpoint Schedule of reinforcement: A translational springboard toward understanding effortful motivation abnormalities in psychiatric disorders. ABSTRACT: The Progressive Ratio Breakpoint Schedule of reinforcement: A translational springboard toward understanding effortful motivation abnormalities in psychiatric disorders. People with psychiatric conditions exhibit abnormal effortful motivational (EM). Quantifying EM in rodents has long-been assessed using tasks with reinforcement-based schedules such as the progressive ratio breakpoint schedule (PRBS). More recently, we have used the PRBS to quantify EM in psychiatric populations. We demonstrated patients with schizophrenia exhibited lower PRBS scores, indicative of lower EM. Importantly, this deficit accounted for 24% of variance of their global cognition scores. In contrast, patients with bipolar disorder (BD) without symptoms of depression exhibited elevated PRBS, indicative of higher EM relative to healthy participants (HC; $F(1,77)=3.7$, $p<0.05$). Reducing expression of Specificity protein 4 (Sp4) reduced the EM of mice (Young et al 2015), while reducing dopamine transporter (DAT) expression elevated EM in mice (Young et al 2019). Hence, psychiatric populations exhibit altered levels of EM, the direction of which can be modeled in mice identifying potential underlying mechanisms. The link between these models remain unidirectional however, developing biomarkers of performance remain vital. Taking this work further, we recently developed EEG-biomarkers of performance of both the PRBS and an effortful decision-making task, the Cognitive Effort Task (CET). We discovered that both humans and mice exhibited elevated posterior alpha power as they began to give up, while interestingly for the CET we observed heightened delta power in those likely to choose easy vs. hard choices, AKA 'slackers' vs. 'workers'. Recently we

tested whether amphetamine increases hard choices in slackers similarly to rats given amphetamine and will discuss these findings. Using the PRBS differential levels of EM can be quantified in psychiatric populations, with patients with schizophrenia and BD exhibiting opposite profiles. Determining whether these differences are reflected in altered EEG biomarkers, and confirming consistency of biomarkers differences in the models, will greatly support their translational relevance. Thus, the development of future therapies from these models will have increased chance for translatibility into patient populations, including developing treatments. SUPPORT: NIMH UH3MH109168

Bolaram A, Coe TE, Power JM, Cheng DT (*Auburn University; University of New South Wales*) Differential delay eyeblink conditioning in humans using perceptually similar conditioned stimuli. ABSTRACT: The role of awareness in differential delay eyeblink conditioning (EBC) has been a topic of much debate. One possible reason for this lack of consensus is that the necessity of awareness for conditioning varies as a function of conditioned stimuli (CS) discriminability. One prediction is that awareness is required for differential delay EBC when two cues are similar. In the current study we tested this view by manipulating the frequencies of auditory CSs in three groups of participants. Group I (easy) received 1000 Hz tones and white noise as CSs, Group II (moderate) received 1000 Hz tones and 1400 Hz tones as CSs, and Group III (difficult) received 1000 Hz tones and 1150 Hz tones as CSs. Both aware and unaware participants showed differential conditioning in Groups I and II, with aware participants in Group II showing conditioning earlier than unaware participants. Aware participants in Group III failed to show conditioning all together. These findings indicate that: 1) awareness is not necessary for differential delay EBC when two tones are easily discriminable, 2) awareness is also not needed for relatively similar tones but may facilitate earlier conditioning, and 3) awareness alone is not sufficient for differential delay EBC.

Boutros SJ, Krenik DK, Holden S, Unni VK, Raber J (*Dept. of Behavioral Neuroscience, OHSU; Jungers Center for Neuroscience; Division of Neuroscience, ONPRC*) Effects of common supplementary cancer treatments on learning and memory ABSTRACT: People undergoing therapy for cancer are afflicted by a host of negative side effects. Deficits in learning and memory are common and debilitating, and can persist after cessation of treatment. Common supplemental medications given during chemotherapy and radiation therapy, such as amifostine (WR-2721) and etoposide, might contribute to cognitive impairments. Amifostine is a reactive oxygen species (ROS) scavenger, decreasing damage to healthy tissue during radiation therapy. However, there is a baseline level of ROS needed in the central nervous system for learning and memory. Etoposide is also commonly co-administered with radiation therapy, killing tumors by inducing DNA damage. Patients receiving these treatments often report CNS side effects; thus, I have started preliminary experiments using amifostine and etoposide to assess their influence on fear learning and memory. Mice received a single i.p. injection of amifostine or etoposide prior to fear training, and their memory was assessed 24h and 2 weeks later. Systemic injections of amifostine revealed an inverted U-shaped curve when fear memory was assessed 2 weeks following training: a middle dose (80.25mg/kg) increased fear memory, while the highest dose (214mg/kg) impaired fear memory. Mice injected with a middle dose of etoposide (35mg/kg) showed persisting fear memory, suggesting an impairment in extinction memory. These preliminary data indicate dose-dependent beneficial and detrimental effects of common cancer treatments on cognitive performance independent of disease.

Broschard MB, Love BC, Kim J, Freeman JH (*University of Iowa*) Role of Medial Prefrontal Cortex in Rat Category Learning ABSTRACT: The process of category learning involves determining which physical features are typical of the category (e.g., category-relevant features) and which features are less exclusive to that category (e.g., category-irrelevant features). Then, attention should be orientated towards the category-relevant features accordingly. Multiple theories of human category learning, for instance COVIS (Competition between Verbal and Implicit Systems) and EpCon (Episodes-to-Concepts), implicate the prefrontal cortex in allocating attention towards category-relevant information. In the current study, we tested this prediction by administering lesions in the medial prefrontal cortex (mPFC) of rats. Then, using a touchscreen apparatus, rats were trained to categorize circular stimuli with black and white gratings that changed in spatial frequency and orientation. Some tasks required attention to one stimulus dimension (rule-based; RB tasks), whereas other tasks required attention to both stimulus dimensions (information integration; II tasks). After 15 training sessions, we examined category generalization by presenting testing sessions containing novel exemplars. We found that compared to sham controls, rats with mPFC lesions were impaired on RB, but not II, tasks. Additionally, fitting the data to the computational model SUSTAIN (Supervised and Unsupervised STratified Adaptive Incremental Network) revealed that the mPFC lesions impaired selective attention for the rats learning RB tasks. Together, these results support human models of category learning that PFC directs attention towards category-relevant information. Future research will examine how mPFC directs attention.

Buhusi M, Griffin D, Lee FS, Buhusi CV (*Psychology, Utah State University; Psychiatry, Weill Cornell Medical College*) BDNF Val66Met Genotype Alters Latent Inhibition of Conditioned Fear ABSTRACT: Brain-derived neurotrophic factor (BDNF) is a growth factor widely expressed in the brain, regulating neuronal differentiation and synaptic plasticity. BDNFVal66Met, a single-nucleotide polymorphism in the human BDNF gene, impairs fear extinction and leads to anxiety-like symptoms. Recent studies have pointed to a role of the BDNF Val66Met genotype in the maturation and function of the fear circuit. Here we investigated the effects of the BDNF Val66Met genotype on the latent inhibition of conditioned fear, a measure of selective attention and learning. No differences in latent inhibition were found between Met/Met and Val/Val mice under baseline experimental conditions: 1 CS-shock pairing, under no-stress conditions. However, following chronic unpredictable stress, BDNF Val/Val mice failed to express latent inhibition, while Met/Met mice continued to show a latent inhibition of conditioned fear. Moreover, stressed Met/Met mice, but not their Val/Val controls, showed increased neuronal activation (number of

cFos positive neurons) in the orbitofrontal cortex and nucleus accumbens shell both key regions in the expression of latent inhibition. Re-evaluation of latent inhibition under no-stress conditions but with an increased number and duration of CS-shock pairings revealed persistent latent inhibition and a similarly increased neuronal activation in the orbitofrontal cortex and nucleus accumbens in Met/Met mice but not in their Val/Val littermates. Our results add latent inhibition to the list of behaviors affected by chronic stress and support a role for BDNF polymorphisms in stress-induced pathological behaviors relevant to schizophrenia and other psychiatric disorders. SUPPORT: NIH AG038767

Bussey T (*University of Western Ontario*) Translation, open science, and data sharing using touchscreen cognitive assessment ABSTRACT: The use of animal models is an indispensable tool for the study of normal cognition, and for understanding and discovering treatments for disorders of attention, memory, and other aspects of cognition, such as those observed in neuropsychiatric and neurodegenerative disease. A major goal in the use of the animal models of cognition is translation, the ability successfully to transfer our behavioural results in animals to studies in humans (and back again). However, the currently most widely used animal behavioural tests are very dissimilar to those used with human subjects, and criticism has been levied at animal research for using methodology that does not translate. The touchscreen method, in which mice and rats interact with an ipad-like touchscreen, provides the ability to test rodents on tasks in many cases identical, in all important respects, to the computerised tests increasingly used in humans. Furthermore some of the touchscreen tests developed in rodents are now being used successfully in human research. By taking such an approach we have a better chance of achieving successful translation from rodent to human in the study of normal cognition, and in discovering treatments for disorders of cognition. In my talk I will illustrate this approach by describing experiments in neurodegenerative and neuropsychiatric disease in mice, rats and humans. I'll also describe touchscreencognition.org, an outward-facing, open-access resource for touchscreen users (now over 300 labs) around the world, including facilitating the combination of touchscreens with e.g., optogenetics and miniscopes, searchable databases, and on-site training.

Chalkia A[1], Vanhasbroeck N[1], Zenses A-K[1], Stemerding L[2], Boddez Y[3], Kindt M[2], Van Oudenhove L[1], Beckers T[1] ([1]*KU Leuven, Leuven, Belgium;* [2]*University of Amsterdam, Amsterdam, The Netherlands;* [3]*University of Groningen, Groningen, The Netherlands*) Directed forgetting of emotional memories ABSTRACT: Declarative memory encoding is sensitive to disruption, and subjects can be cued to intentionally "forget" information before it is stored using a directed forgetting (DF) manipulation. Until now, DF has been applied in declarative memory procedures only. Here, we report on a novel fear conditioning procedure aimed to investigate whether this technique can be translated to the study of emotional memories. In a first study, 32 simple line drawings were displayed one at a time, and half of them were followed by an aversive image (CS+), while the other half were not (CS-). An acoustic cue was presented after half of the CS+ and CS- trials, indicating that those trials were to be forgotten. Memory retention was assessed in subsequent free recall and recognition tasks. In line with predictions, we found strong, significant main effects of instruction ($p < .001$), with subjects recalling and recognizing fewer of the items that were followed by the forget cue. In a follow-up study, we slightly modified our procedure by presenting an aversive image following CS+ items and a neutral image following CS- items, and still retained our significant main effects of instruction on both tests of memory retention. In a third study we modified our protocol to include physiological measures, and this time, CS+ items were followed by a mild electric shock US, while CS- items were never paired with shock. Skin conductance (SCR) was included as an index of fear responding. Once again, we observed a main effect of instruction on declarative memory performance. Moreover, we observed differential acquisition of fear in SCR, and an attenuation of SCR only in response to CS+ items that were instructed to be forgotten. Altogether, our findings provide novel evidence for the presence of a DF effect at a declarative and physiological level of emotional memory and suggest that DF manipulations can be successfully used to interfere with emotional memory encoding.

Clark L (*University of British Columbia*) Operant influences in realistic slot machine gambling ABSTRACT: Slot machines are increasingly recognized as one of the most harmful forms of gambling; for example, they are typically the most common preferred form of gambling among treatment-seeking individuals with Gambling Disorder. Modern slot machines are sophisticated gambling products in which an array of psychological variables ('structural characteristics') has been optimized to promote risky and continuous behaviour. This talk will consider the impact of these product features, studied in the lab in experiments using both authentic and simulated slot machine games. One recent experiment (Chu et al 2018 International Gambling Studies) examines how regular slot machine gamblers deploy the 'stopper button', an operant device that allows the gambler to brake the spin, but without affecting their likelihood of winning. Stop button use was associated with faster spin initiation latencies, and also increased following spins on which the use of the stop button coincided with a win. However, the use of the stop button was not associated with cognitive beliefs regarding its effectiveness. In a second experiment (Ferrari et al, in prep) we have examined the expression of automaticity in slot machine gambling, as a window on habit formation. Over three sessions, novice gamblers increased their pace of gambling, and reduced the variation in bet size, both within and across sessions. These effects were not associated with self-reported 'immersion' in the game, which decreased across sessions. The results will be considered in relation to the role of habit formation in addictive behaviors, and regulatory implications for the development of new forms of gambling including 'skill-based' games.

Cole KE, Lee J, Parsons RG (*Stony Brook University, NY*) Subthreshold fear conditioning produces a rapidly developing neural mechanism that primes subsequent learning ABSTRACT: Prior experiences have the ability to alter the nature of and capacity for future learning. Therefore, identifying the mechanisms that allow prior experience to affect future learning is important in understanding how memories are formed. We have previously shown that a single fear conditioning trial, which on its own does not support long-

term memory, primes future learning such that when an identical trial is delivered within 60 minutes or 24 hours, a robust memory is formed. Here, we set out to determine whether or not manipulating neural activity in the amygdala using designer receptors exclusively activated by designer drugs (DREADDs) shortly before or immediately after the initial learning trial would affect the ability of that initial trial to prime future learning. Rats were bilaterally injected with an adeno-associated viral vector expressing a modified form of the human muscarinic receptor M4, hM4Di (AAV8- CaMKII-hM4Di-mCherry) or a control virus (AAV8-CaMKII-eGFP) of the same promoter and serotype, into the BLA. Rats were then fear conditioned with 2 trials spaced by 24 hours. Before the first trial, rats infected with either the inhibitory DREADD receptor hM4Di or control virus were given systemic injections of clozapine-N-oxide (CNO), an inert ligand required to activate the inhibitory DREADD. A third group of rats expressing hM4Di were given injections of the vehicle at the same time point. A second identical trial followed 24 hours later, and memory was tested 48 hours after the final trial. Our results show that inhibiting the amygdala prior to, but not immediately after, the first trial prevented the initial learning from priming future learning. Subsequently, we blocked amygdala activity immediately after the initial training trial by pharmacological inhibition of protein kinase A and mitogen activated protein kinase A; both known to have a more established effect on memory consolidation. Similar to DREADD inhibition, we found that targeting either kinase had no effect on the ability of the initial trial to prime subsequent learning. Together, these results indicate that the neural mechanisms that allow a weak learning event to alter subsequent learning develop rapidly and do not require a post-learning consolidation period. SUPPORT: Center for Inclusive Education

Colon LM, Poulos AM (*University at Albany, SUNY*) Role of neonatal and pubertal gonadal hormones in the organization of context fear conditioning.. ABSTRACT: Our previous research demonstrated a developmentally divergent pattern of context mediated freezing, such that context fear expression in male Long Evans rats increases from pre-adolescence into adulthood while context fear in females decreases from pre-adolescence into adulthood (Colon et al, 2018). This pattern may suggest that gonadal hormones play a role in organizing the neural systems underlying contextual fear conditioning. In rats, in the hours after birth, males show a spike in circulating testosterone (Döhler & Wuttke, 1975; Bell, 2018). After postnatal day 2, steroidogenesis of the testis are quiescent until puberty where testosterone increases dramatically between P40 and P60 (Döhler & Wuttke, 1975; Bell, 2018). In females, steroidogenesis of the ovary is minimal at birth and maintained at very low concentrations until P39, after which estradiol and progesterone begin circulating in high concentrations with fluctuations in these hormones every 4 days (Döhler & Wuttke, 1975; Bell, 2018). Steroidogenesis of gonadal hormones in male and female rats suggest there are two key postnatal periods in which gonadal hormones might organize the brain in male rats and one key postnatal period in females. The aim of this study is to investigate the potential role of early circulating gonadal hormones in organizing the neural systems underlying contextual fear conditioning. In order to determine whether or not neonatal gonadal hormone exposure and/or pubertal gonadal hormone exposure organizes the neural systems underlying context fear conditioning, we conducted two behavioral experiments. In experiment 1 we removed the testis within 8 hours on the day of birth (P0), and fear conditioned male Long Evans rats either 24 (pre-adolescence) or 60 (adult) days later. In experiment 2, prior to puberty at P28, we removed either the testis or the ovaries, in males and females respectively, and fear conditioned male and female Long Evans rats 32 days later at P60. Our preliminary findings indicate that gonadectomy alters the expression of contextual fear compared to control subjects, suggesting that gonadal hormones have an organizational influence on the neural systems underlying contextual fear conditioning. SUPPORT: 1R01MH114961 (AMP)

Conoscenti MA, Fanselow MS (*Integrated Center for Learning and Memory, Brain Research Institute, Department. of Psychology, UCLA, Los Angeles, CA; The Staglin Center for Brain and Behavioral Health, UCLA, Los Angeles, CA*) Chronicity of stress modulates its behavioral and neurobiological consequences ABSTRACT: An acute traumatic event can lead to life-long changes in stress susceptibility and result in psychiatric disease, such as Post-Traumatic Stress Disorder (PTSD). The stress literature is characterized by the use of a diverse array of stressors that have equally diverse effects on behavior and physiology. There is considerable interest in what aspects of stress (e.g., severity and chronicity) are important in producing pathology. Unfortunately, the field's tendency to use a wide variety of stressors, most of which are neither quantifiable nor directly comparable, have led to a state where no clear conclusions can be drawn. Virtually every study that attributes an effect of stress to its chronic nature includes no contrast with acute stress, or confounds chronicity with severity. In the current study we sought to investigate the behavioral and neurobiological consequences of chronic versus acute stress. To do so, we have equated severity and exposure by simply breaking up our acute stress preparation over 15 days. We exposed 50 Long-Evans rats to 15, 1mA footshocks, or context exposure without shock. This occurred over 15 consecutive days (1 shock per day), or within a single session. In this way most experimental parameters (e.g., number of shocks, total stress context exposure), except for chronicity, were equated. Rats in each condition had 6-hours access to a 40% glucose solution or water immediately following termination of each session. Following the 15 days of exposure, all animals underwent 6 days of 30-minute preexposure in a novel context. The day following preexposure, all rats were exposed to 1, 1mA footshock in a novel context and were tested for freezing in that same context 24-hours later. Forced swim testing occurred on the two days following the final context exposure. Four days later rats were sacrificed using isoflurane and decapitated. Brains were extracted for future Western Blotting analysis. We found that animals that received chronic stress exhibited higher levels of persistent fear generalization across preexposure sessions when compared to their acutely-stressed counterparts. Chronically-stressed rats also exhibited higher levels of freezing during the final context test. No differences were observed between groups in the forced swim task. Glucose appeared to enhance fear generalization across preexposure sessions, and enhance freezing during the final context test, in rats that received chronic, but not acute, stress. These data suggest that chronic and acute stressors may produce a heterogeneous phenotype and involve dissociable neurobiological mechanisms. Future studies that further investigate the central and peripheral processes differentially engaged by chronic and acute stress could pave the way for targeted psychiatric inter-

ventions that take into account the chronicity of the inciting stressor. SUPPORT: This research was supported by NIMH R01MH115678 and The Staglin Center for Brain and Behavioral Health.

Cooke MB, O'Leary TP, Harris PK, Brown R, Snyder JS (*University of British Columbia*) Pathfinder: open source software for analyzing spatial navigation search strategies ABSTRACT: Spatial navigation is a universal behavior that varies depending on goals, experience and available sensory stimuli. Spatial navigational tasks are routinely used to study learning, memory and goal-directed behavior, in both animals and humans. One popular paradigm for testing spatial memory is the Morris water maze, where subjects learn the location of a hidden platform that offers escape from a pool of water. Researchers typically express learning as a function of the latency to escape, though this reveals little about the underlying navigational strategies. Recently, a number of studies have begun to classify water maze search strategies in order to clarify the precise spatial and mnemonic functions of different brain regions, and to identify which aspects of spatial memory are disrupted in disease models. However, despite their usefulness, strategy analyses have not been widely adopted due to the lack of software to automate analyses. In order to address this lack of software, we developed Pathfinder, an open source application for analyzing spatial navigation behaviour. In this poster we show Pathfinder's performance on a simple dataset, where it effectively characterized highly-specific spatial search strategies used during the trials. Our software provides support for inputs from commonly-used, commercially-available and open-source software packages, is optimized for classifying search strategies (Direct Swim, Focal Search, Directed Search, Spatial Indirect, Chaining, Scanning, Random Search, Thigmotaxis), and can also be expanded easily to work with other species and spatial navigation tasks. Pathfinder has the ability to automatically determine the platform location as well as the size of the pool and related pool parameters.ÂăÂăIt can generate heatmaps of trials, analyze navigation with respect to multiple goal locations, and due to the open source nature of the project, can be easily updated to accommodate future developments in spatial navigation behaviours.

Cushman JD, Drew MR, Krasne FB (*JDC: NIEHS-NIH; MRD:Center for Learning & Memory, Dept Neurosci, UT Austin; FBK: Dept Psychol & Brain Res Inst, UCLA*) The Environmental Sculpting Hypothesis of Postnatal Hippocampal Neurogenesis ABSTRACT: We propose that a major contribution of postnatal neurogenesis (PNN) is to allow postnatal experience to sculpt dentate gyrus (DG) connectivity such that sensory attributes that are relevant to the animal's environment are more strongly represented. This "specialized" dentate is then able to store a larger number of discriminable memory representations. Our hypothesis draws on Marr's Theory of Archicortex and its derivatives, which postulate that when a memory is encoded, the DG cells that are most richly innervated by the cortical cells corresponding to the to-be-remembered experience fire and drive specific CA3 followers, which, together with the DG cells themselves, may be considered the experience's hippocampal "representation." In such a scheme, memory coding improves as the set of DG cells from which a representation is chosen increases. This occurs because the larger the pool of DG representation cells innervated by cortical neurons that might actually fire, the less will be the overlap between one representation and another and the richer will be representation cell innervation by the active cortical cells of the to-be-remembered experience. Reduced representation overlap and richer innervation in turn allow more memories to be stored and accurately recalled without significant interference amongst them. We posit that granule cells born in early development, prior to significant behavioral experience, likely include many cells innervated by cortical neurons that are not activated by stimuli the animal is likely to experience. In contrast, because the survival and innervation of postnatally-born neurons is shaped by behavioral experience, PNN increases the number of DG neurons that are innervated by cortical cells actually liable to fire during experiences needing to be remembered. In this poster we spell out the above arguments more fully and present computational simulations demonstrating that sculpting should enhance memory storage capacity and recall accuracy. Finally, we discuss published evidence relevant to our proposal and describe novel, testable hypotheses that it generates. SUPPORT: R01 MH102595, R01 MH117426 to MRD

Debiec J, Chang D-J, Numbers S, Hider J, White A (*University of Michigan*) The ontogeny of the observational threat learning through scream sounds ABSTRACT: Social transmission of threat may occur through instructional or vicarious threat learning and is present as early as in infancy. During observational threat learning, animals acquire defense responses to cues signaling danger through observation of a conspecific expressing fear to these cues. Although in many species one of the most powerful modes of expressing fear to immediate threat is scream, little is known about the role of scream sounds in early social fear learning. Here, using a rat model we show that infant pups acquired fear to a novel odor if this odor was paired with prerecorded and played back maternal scream sounds. Exposure to maternal scream sounds elevated infant's plasma levels of the stress hormone corticosterone and increased amygdala activation measured by c-Fos early gene expression. Disruption of the maternal scream sounds-induced corticosterone rise abolished the increase of c-Fos expression in the amygdala and disrupted fear transmission. Our results demonstrate that maternal scream sounds trigger an infant's stress response and activate the amygdala, and reinforce associative threat learning. Elucidating neurobiological mechanisms of early social threat learning will contribute to our understanding of intergenerational transfer of adaptive and maladaptive fears, such as in phobias or posttraumatic stress. SUPPORT: K08 MH014743-01A1, NARSAD Young Investigator Award from the Brain & Behavior Research Foundation

Desrochers SS, Nautiyal KM (*Psych and Brain Sciences, Dartmouth College*) A convergent role of serotonin signaling in conditioned inhibition and instrumental response inhibition ABSTRACT: Traditionally, the behavioral and neural mechanisms of Pavlovian conditioned inhibition have been studied separately from operant response inhibition and paradigms aimed at measuring impulsive action. Given our recent studies implicating serotonin signaling in the neural basis of impulsive action (both waiting and withholding responses), we hypothesized that the same neural circuits would also influence conditioned inhibition. Using genetic and pharmaco-

logical manipulations of serotonin signaling at the 5-HT1B and 5-HT2C receptors, we tested the idea that manipulations which result in impairments in classically defined impulsive action tasks would also result in deficits in conditioned inhibition. Using a tissue-specific and inducible 5-HT1B receptor knockout mouse (tetO construct), we show decreased inhibition in a conditioned inhibition paradigm that parallel those seen in a Go/No-Go task. Specifically, mice lacking 5-HT1B receptor expression showed increased responding to the CS+/inhibitor pairings during training and decreased suppression of responding to the inhibitor / transfer-excitor compound in the summation test, compared that seen in normal control mice. They also showed decreased responding to the inhibitor/US pairing in the retardation of acquisition test. Current studies are aimed at assessing the effect of pharmacological manipulation of 5-HT2C signaling on conditioned inhibition given its extensively studied role in operant response inhibition paradigms. Our studies suggest that serotonin signaling, while not normally implicated in conditioned inhibition, does play a role in the expression of inhibitory associations. Overall, evidence demonstrating that the same manipulations influence both conditioned inhibition and impulsive action suggests that there are overlapping neural circuits controlling inhibitory mechanisms that contribute to the inhibitory processes in both Pavlovian and instrumental paradigms. SUPPORT: [NIH R00 MH106731]

Dowell JR, Datuin E, Escobar M (*Oakland University*) Amelioration of Spatial Memory Deficits in Rats Receiving Early Prenatal Exposure Alcohol ABSTRACT: Alcohol use during pregnancy can lead to Fetal Alcohol Spectrum Disorders (FASDs), which are characterized by an array of cognitive, physical, and developmental disabilities. Some of the deficits observed in children with FASD resemble those observed in neurodegenerative disorders in aging individuals, which may be ameliorated by infusion of the protein Brain Derived Neurotropic Factor (BDNF). 7,8 dihydroxyflavone (7,8-DHF) is a potent agonist for the BDNF receptor Tyrosine kinase B, supplementing the protein. In the present study, we examined the degree to which administration of 7,8-DHF would attenuate spatial memory deficits in a rodent FASD model. Dams consumed moderate levels of alcohol from day 2 of pregnancy until the day of parturition, a gestational period equivalent to the first two trimesters of human pregnancy. Chronic administration of 7,8 DHF during periadolescence (PND 15-30) resulted in increased general activity and exploration in a Y-maze task, thus reducing some aspects of the spatial deficits otherwise observed in FASD rats.

Dulka BN, Trask S, Helmstetter FJ (*University of Wisconsin-Milwaukee*) The Effects of Aging on Memory and Activity-Driven Protein Degradation ABSTRACT: Aging is accompanied by an accumulation of damaged and modified proteins in neurons. This buildup of altered proteins is the result of a gradual deterioration of both cellular quality control mechanisms and decreased protein degradation processes. The ubiquitin-proteasome system (UPS) is the primary proteolytic mechanism responsible for the degradation of damaged proteins. Additionally, a growing body of literature highlights the important role the UPS plays in the regulation of memory and synaptic plasticity; however, the role of the UPS and protein degradation processes in age-related cognitive decline remains poorly understood. In the current study, we investigated several endpoints related to activity-driven protein degradation that we have previously shown to be important for synaptic plasticity and related them to memory performance in rats as a function of both age and sex comparing 3-, 15- and 22-month old rats. We first found that 22-mo old males show deficits in the retention of a trace fear conditioning (TFC) memory. Female rats, although they froze less than males overall, displayed no obvious effect of age in this task. We next focused on brain areas critical for TFC including the basolateral amygdala (BLA), dorsal hippocampus (DH), and medial prefrontal cortex (mPFC). Using western blots we quantified proteins related to the UPS including phosphorylation of the Rpt6 proteasome regulatory subunit (pRpt6) and lysine-48 (K48)-linked ubiquitin tagging. Not only did 22-mo old males display significantly less phosphorylated Rpt6 in the BLA compared to younger males, but we also found that male rats classified as impaired in TFC memory retention had decreased BLA pRpt6 protein compared to those rats classified as unimpaired. A corresponding increase in K48 polyubiquitination was also observed within the BLA of 22-mo old males. Increases in K48 expression were also observed in 22-mo old males within the DH. Interestingly, both 15- and 22-mo old females displayed increases in K48 polyubiquitination within the mPFC. Altogether, this research extends our understanding of the relationship between the UPS, aging, and memory, which is an important first step toward the prevention and treatment of normal cognitive aging, as well as memory-related neurodegenerative diseases. SUPPORT: NIH R21AG053854

Dybing K, Faruqi W, Aguilera J, Dahlberg L, Rose J (*Behavioral Neuroscience Program, Western Washington University, Bellingham, WA*) Long Term Memory for Associative Conditioning and Glutamate Receptor Expression. ABSTRACT: Pharmacological and behavioral studies indicate glutamate plays a central role in long-term memory (LTM). C. elegans have orthologs for glutamate receptors (e.g., nmr-1 and glr-1). Using mutant strains, we investigated the role of glutamate receptor signaling in LTM for associative conditioning in C. elegans. For this research, we utilized a spaced associative training protocol pairing discrete stimuli (mechanosensory stimulation (vibration) and blue light (470nm)). Animals were given 5 blocks of training at a 12-minute interblock interval with each block consisting of 5 stimulus pairings (at a 60s ISI). Behavioral tests measured the animals' locomotor responses to a single vibration stimulus 24 hours after training. Using GLR-1::GFP transgenic animals, glutamate receptor expression levels were measured 24 hours after training in both wild-type and mutant backgrounds. Results indicate proper glutamate receptor expression is necessary for LTM.

Ehlers MR, Todd RM (*University of British Columbia*) Hedonic but not sensory experiences are reactivated with Pavlovian conditioning ABSTRACT: Many years of research on emotional learning processes in non-human animals has established neural and behavioral mechanisms of Pavlovian conditioning. Yet, in humans, there remain longstanding questions about the nature of the information that comes to be associated with salient events. Here we leveraged contemporary methods in human brain imaging data analysis to resolve questions that have been debated for decades:

Do neural responses to a conditioned stimulus (CS) represent the sensory properties of an unconditioned stimulus (US) or do they represent its hedonic valence âĂŤthe painful and pleasurable qualities? Functional magnetic resonance imaging (fMRI) data was collected from 61 healthy young adults during a Pavlovian learning task pairing pressure pain or pleasant touch with individual faces. Data was analyzed using representational similarity analysis (RSA), an approach that probes brain activation patterns in an abstract and multidimensional space that allows modeling of underlying content. Results showed that in primary sensory regions, sensory information about the US was not reactivated in response to the CS+. Yet in hubs of networks sensitive to affective salience, such as the ventromedial prefrontal cortex, hedonic information about the pleasant or aversive qualities of the US were reactivated by the CS+ after associations were learned. We conclude that, with Pavlovian conditioning, it is the hedonic but not tactile information about the US that is carried forward with learning. SUPPORT: CIHR; Michael Smith Foundation for Health Research

Ehlers VL, Yousuf H, Smies CW, Moyer JR (*University of Wisconsin - Milwaukee*) Ventral hippocampal neuronal excitability and immediate early gene expression following trace fear learning. ABSTRACT: Associative learning triggers neuronal plasticity in brain regions that are critical for storing and retrieving memory. Trace fear conditioning is an associative learning paradigm that induces plasticity in several brain regions, including the amygdala, prefrontal and retrosplenial cortices, and the dorsal hippocampus. One region whose role in trace fear learning and memory remains elusive is the ventral hippocampus (VH). Due to its proximity to and connections with other brain regions involved in the fear circuit, VH is well-suited to support trace fear learning. Indeed, several inactivation and lesion studies suggest that VH has a major role in this learning task. Trace fear learning is disrupted following excitotoxic lesions of VH (Yoon & Otto, 2007), or when VH is inactivated using the GABAA agonist muscimol (Czerniawski et al., 2009). VH may also be involved in maintaining long-term trace fear memory, as trace fear expression is impaired when VH is inactivated up to 42 days after training (Cox et al., 2013). These studies suggest there could be a definitive role for VH in supporting associative trace fear learning. However, there is currently very little understanding of how trace fear learning can alter VH plasticity. By examining immediate early gene (IEG) expression using Western blots, as well as intrinsic excitability using whole-cell patch-clamp electrophysiology, our lab is exploring how trace fear learning affects VH plasticity. Adult male F344 rats (3 mo.) were randomly assigned to one of four behavioral groups: 1) home-cage (NAIVE), 2) pseudoconditioning (PSEUDO), 3) trace fear conditioning (TRACE), or 4) context fear conditioning (CTXT). Animals underwent a single training session on day 1, followed by a brief behavioral test on day 2. In vitro patch-clamp recordings of brain slices from CTXT animals suggest trace fear learning increases spiking activity of VH CA1 neurons. Western blot analysis also suggests Arc expression is elevated in VH of CTXT animals, while Zif-268 is elevated in VH of TRACE and CTXT animals. The extent to which neuronal IEG expression co-varies with changes in the excitability of those neurons to represent circuit-specific (e.g., context vs trace memory) is currently unknown. These findings suggest that neuronal plasticity within VH is altered following acquisition and/or retrieval of trace and context fear conditioning.

Escobedo A, Lee CHL, Sowinski EM, Herakovich R, Sangha S (*Department of Psychological Sciences, Purdue University & Purdue Institute for Integrative Neuroscience*) Effects of the partial NMDAR agonist D-Cycloserine on the acquisition of discriminative safety learning and consolidation of fear extinction ABSTRACT: Individuals suffering from posttraumatic stress disorder (PTSD) have difficulty maintaining reduced fear levels after extinction-based therapies, as well as reducing fear levels in response to explicit safety cues. Prior research has shown that the partial NMDA receptor agonist, D-Cycloserine (DCS), can facilitate the acquisition and consolidation of fear extinction in humans and rodents. However, it is unclear if this facilitation is limited to non-discriminative fear paradigms, where the subject first learns to fear a cue which is then later extinguished, or if it can also facilitate discrimination between a fear cue and a safety cue. The present study examined the effects of DCS in adult male Long Evans rats during a fear, safety, and reward cue discrimination conditioning task, as well as its effect on subsequent fear extinction. We hypothesized that DCS would facilitate discrimination learning between a fear cue paired with shock and a combined fear+safety cue presented without a footshock, and this facilitated discrimination would then facilitate subsequent fear extinction. DCS (30.0 mg/kg i.p) was administered 30 min prior to each discrimination learning session, which resulted in marginally greater fear inhibition during the fear+safety cue versus the fear cue; however, this improved discrimination did not facilitate subsequent drug-free fear extinction. In a separate group we tested the hypothesis that DCS would facilitate the acquisition and consolidation of fear extinction in non-discriminative fear learning based on prior research. After fear conditioning to a single fear cue, DCS was administered either directly before fear extinction or directly after, to assess its effect on acquisition versus consolidation. In neither case did we see improved extinction retention one day later. Together, our data indicate that DCS provides only mild improvement on inhibiting fear in the presence of a safety cue, and does not facilitate the acquisition or consolidation of non-discriminative fear extinction.

Fanselow MS (*UCLA*) Advantages of titratable stressors and quantifiable behavioral indicators in revealing the impact of stress. ABSTRACT: The stress literature is characterized by the use of a myriad of stimuli affecting many modalities often with several modalities mixed together. Many of these studies also suffer from the fact that there is no dependent measure that gives a clear and scalable read-out of the effectiveness of the manipulation. At its core, Stress-Enhanced Fear Learning (SEFL) uses a single modality (shock) that is easily titratable and freezing provides a quantitative indicator of the impact of stress. I will describe a potpourri of experiments that exploit these features. The experiments show that to produce SEFL the stressor must be intense, but the consequences of that stress generalize to learning about other aversive stimuli. Furthermore, enhanced learning generalizes to the reinforcing properties of opioids. While the typical SEFL stressor (15 shocks over 90 min) produces SEFL in almost all animals, downward titration of the stressor (4 shocks) reveals a bimodal distribution of susceptible and resilient subjects that approximates the rates of Post-Traumatic

Stress Disorder found in humans that have experienced traumatic stress. By exploiting the parametric features of SEFL we are also able to distinguish, for the first time, between the effects of chronic and acute stress in a manner that is not confounded by stress severity. SUPPORT: R01MH115678, R01AA026530, P50DA005010, Staglin Center for Brain & Behavioral Health

Farley SJ, Freeman JH (*The University of Iowa, Iowa Neuroscience Institute*) Optogenetic stimulation of amygdala central nucleus efferent pathways modulate cerebellum-dependent learning ABSTRACT: Amygdala output is known to play a modulatory role in cerebellum-dependent learning (Farley 2016, 2017, 2018). Pharmacological inhibition of the amygdala central nucleus (CeA) results in a reliable impairment acquisition and retention of the cerebellum-dependent delay eyeblink conditioning (dEBC) in adult rats. Further, optogenetic inhibition of CeA neurons that is temporally synced with the onset of the conditioned stimulus (2KHz tone) impairs acquisition (Farley 2018). It is unknown if amygdalar modulation of the cerebellum acts through one or multiple CeA efferent pathways. In this study, we optogenetically targeted three efferent pathways of the rat CeA that may modulate cerebellar dependent learning. An inhibitory optogenetic vector (AAV5-hSyn-eArch3.0-EYFP) was bilaterally delivered to the CeA. Five weeks after viral injection optical fibers were placed in CeA neuron terminal fields of one of three projection targets: basilar pontine (PN), locus coeruleus (LC), or ventral lateral periaqueductal grey (vlPAG). Photo-stimulation with a 561 nm laser was limited to the duration of the CS only. Controls animals were injected with an opsin-lacking AAV (AAV5-hSyn-EYFP). After recovering from optical implant surgery, rats commenced training in five, 100-trial sessions of dEBC. Trials consisted of paired tone (conditioned stimulus [CS]) and peri-orbital shock (unconditioned stimulus [US]). Optogenetic inhibition of the targeted CeA efferent pathways revealed differential effects on acquisition of dEBC. Inhibition during the CS period of the CeA-PN projection or the CeA-LC projection impaired the rate of conditioned responses (CRs). However, CRs were not impaired in animals receiving inhibition of the CeA-vlPAG projection or the control group. Conversely, the amplitude of the CR was impaired for animals receiving inhibition of the CeA-vlPAG projection, yet inhibiting the CeA-PN projection or the CeA-LC projection did not impair CR amplitude. Inhibiting the CeA-vlPAG projection or the CeA-LC projection reduced the amplitude of the unconditioned response relative to controls, but was not impaired inhibiting the CeA-PN projection. These results suggest CeA efferent projections contribute to different aspects of cerebellum-dependent associative learning. SUPPORT: National Institute of Neurological Disorders and Stroke grant NS088567

Ferrara NC, Padival M, Loh M, Rosenkranz JA (*Rosalind Franklin University*) Brief social isolation increases social interaction and cortical drive of basolateral amygdala activity. ABSTRACT: Adolescence is characterized by high social drive and ongoing brain maturation. The decline in social drive from adolescence to adulthood coincides with cortical development, which likely influences the age-dependent changes in the regulation of emotions. Increased activity in cortical regions, such as the anterior cingulate cortex (ACC), and the amygdala have been linked to social behaviors, and the projections from the ACC to the basolateral amygdala (BLA) are necessary for socially learned fear. Combined, this suggests developmental changes in the ACC-BLA pathway regulating social drive. Manipulations of social drive can be used to investigate the developmental shifts in social behaviors and uncover role of the ACC and BLA. Brief social isolation facilitates social drive and promotes the value of social interactions. This approach was used to investigate whether the ACC-BLA circuit might contribute to developmental changes of social behaviors. We found that brief social isolation (2hrs) increases the duration of social interaction, in adolescents and adults, and the overall duration of social interaction was substantially higher in adolescents. We next used anesthetized in vivo single unit recordings to determine the impact of brief isolation on BLA activity in adults. We found that brief isolation increased BLA neuronal activity. Futher, ACC-evoked BLA activity was preferentially increased in groups exposed to brief isolation. Because increased BLA excitability might produce a global increase in BLA-dependent behaviors, we measured effects of brief social isolation on classical fear conditioning. However, the increase in BLA activity and social interaction as a result of isolation did not influence fear learning and memory retention, suggesting changes in BLA activity were not generalized to all BLA-dependent behaviors. These results suggest that increased social drive, caused by brief isolation, may selectively influence social behaviors,and facilitate ACC influence on BLA activity in adults. These results begin to provide insight to the changes in cortico-BLA circuitry from adolescence to adulthood that contribute to the refinement of social behaviors. SUPPORT: NIMH R01 MH118237

Fisher H, Pajser A, Pickens CL (*Kansas State University*) Prelimbic cortex inactivation during training does not impair later devaluation in a cued-trial multiple-response/multiple-reinforcer operant devaluation task in rats. ABSTRACT: Devaluation is a task often used to model flexible goal-directed action, the ability to adaptively modify behavior when the value of a reinforcer changes. In an experiment with pre-training inactivations, we previously found that basolateral amygdala (BLA) and mediodorsal thalamus (MD), but not orbitofrontal cortex (OFC), were necessary to learn the initial information needed to guide later devaluation. Due to the parameters of our cued-trial multiple-response/multiple-reinforcer operant devaluation task, rats could either use stimulus-outcome (S-O) associations using the unique cuelights above each lever or response-outcome (R-O) associations using the spatial lever location to maintain goal-directed action. Here, we tested male Long Evans rats (n=24) in a cue-switching experiment to determine the strategy rats use to complete our task (attending to the discrete light cue or spatial lever location). In the Cue Normal group, the rats received the same lever-light compound configurations in the devaluation test as during training. In the Cue Switched group, the cuelights above the levers were switched during the devaluation tests compared to their position in training. Both groups exhibited a devaluation effect based on the lever location, suggesting rats without neurobiological manipulations rely on the spatial lever location to guide behavior in our devaluation task. Because rats primarily use an R-O strategy, putatively mediated by the prelimbic cortex (PL), we then sought to determine whether PL was required for learning the initial information required for future goal-directed action in our task. In male and female Long Evans rats (n=68), we inactivated PL during

initial training and found that both the PL inactivation and control groups showed a devaluation effect. The lack of OFC and PL involvement in our task, despite rats naturally preferring a presumably PL-mediated strategy, suggests that rats can compensate for loss of PL function by using S-O associations, presumably supported by OFC, to guide goal-directed action in our task. Future studies will verify that OFC and PL can compensate for each other to maintain intact goal-directed action in our task when the functioning of one of them is impaired. SUPPORT: This work was supported by the National Institutes of Health [grant number P20 GM113109-01A1].

Floresco SB (*University of British Columbia*) Ventral Striatal Circuits Underlying Different Aspects of Aversively Motivated Behavior ABSTRACT: Flexible expression of motivated behavior requires mechanisms to promote or inhibit output depending on different motivational states, and dysfunction in neural circuits mediating these functions may underlie maladaptive behaviors associated with various mental illnesses. The contribution of different subregions of the nucleus accumbens (NAc) and its input from the medial prefrontal cortex (mPFC) to promoting and modifying appetitive behavior are well established, yet how these circuits regulate aversively-motivated behavior in situations involving response conflict has been underexplored. We examined the contribution of the NAc shell and core and some of their inputs to two distinct aspects of aversively-motivated behavior: discriminative fear-induced suppression of reward seeking and active/inhibitory avoidance. Inactivation of the NAc shell or disruption of mPFC-NAc circuitry blunted fear expression to a shock-associated tone (indexed by conditioned suppression of lever pressing for food) without affecting responses to a neutral stimulus, whereas NAc core inactivation reduced reward seeking without affecting Pavlovian fear. Active/inhibitory avoidance was assessed with a novel, instrumental go/no-go task. Rats learned to discriminate between two 15 s tones signaling shock could be avoided if they either pressed a lever (active avoidance) or withheld pressing (inhibitory avoidance). Inactivation of the NAc core or prelimbic mPFC selectively disrupted active, but not inhibitory avoidance. In contrast, inactivation of the shell or ventral infralimbic mPFC impaired active and inhibitory avoidance. However, only infralimbic (but not prelimbic) mPFC facilitated performance of a simpler active-avoidance-only task that did not require shifting between initiating/withholding responses. Collectively these data indicate that neural circuits interlinked with NAc shell play a broad and complex role in regulating aversively-motivated behavior, inhibiting inappropriate or punished behavior and promoting active avoidance. In comparison, NAc core-prelimbic PFC circuits control instrumental avoidance in situations requiring response flexibility. These findings provide insight into how dysfunction in prefrontal-ventral striatal circuitry may contribute maladaptive responses to threat or punishment in disorders such as anxiety, substance abuse and behavioral addictions. SUPPORT: Natural Sciences and Engineering Research Council of Canada

Freeman JH (*University of Iowa*) Category Learning in Rats ABSTRACT: Category learning is fundamental to memory organization. Categories are equivalence classes based on perceptual similarity or conceptual relations. Categorization in turn facilitates identification and evaluation of novel stimuli. Our studies of rat visual category learning have used a touchscreen apparatus in which rats touch an infrared touchscreen to solve various tasks. We have found that rats learn categories from photographic stimuli, artificial stimuli consisting of arbitrary features, and stimuli that differ in one relevant dimension (rule-based, RB) or multiple dimensions (information integration, II). Theories of category learning posit different roles for the medial prefrontal cortex (PFC), hippocampus, and striatum. We are examining the respective roles of these areas in category learning using lesions, inactivation, multisite neurophysiology, and computational modeling. The findings indicate that the PFC, anterior cingulate, hippocampus, and dorsal striatum interact to support category learning. SUPPORT: P01 HD080679

Gallo M, Hamid AA, Ofray D, Shleifer D, Hrabarchuk E, Bath KG (*Brown University*) Effects of early life adversity on motivational vigor and striatal dopamine function in female mice ABSTRACT: Early life adversity (ELA) is associated with increased lifetime risk for reward-related psychopathologies, which are more common in females. The effects of ELA on the development of reward motivated behavior or their neural underpinnings remain poorly understood. Here, we used a mouse model of resource restriction (limiting nesting and bedding) to alter maternal care for pups, promoting ELA in pups. We hypothesized that unpredictable early care may contribute to altered development of expectations for future reward contingencies and risk for reward-related pathology across the lifespan. We observed that ELA promoted changes in the expression of dopamine receptor subtypes in the striatum, suggesting that reward leaning circuits may become perturbed. Specifically, we found ELA associated overexpression of dopamine receptor (DR) D3 in ventral striatum and under expression of DRD1, indicative of possible disturbance in function of reward related striatal pathways. To determine the behavioral implications of these molecular changes, we used a progressive ratio task to assess changes in motivation for reward in ELA and control female mice. Indeed, exposure to ELA altered effort investment and vigor to work for a reward in females, as evidenced by altered patterns of lever pressing in this task. Our findings help to further our understanding of critical effects of ELA on reward processing and possible neural underpinnings of altered risk for pathological behaviors.

Glanzman D (*University of California Los Angeles*) Synaptic plasticity and long-term memory: An uncertain relationship ABSTRACT: The prevailing hypothesis in neuroscience, the synaptic plasticity and memory (SPM) hypothesis, holds that consolidated long-term memories are stored as stable alterations in the efficacy of synaptic connections. But recent results from our laboratory using a simple invertebrate model, the marine snail Aplysia, have raised questions about this hypothesis. We have found that the maintenance of long-term memory (LTM) does not appear to depend on the persistence of specific synapses induced during learning; rather, it depends on ongoing DNA methylation. In addition, we have found LTM can be restored following disruption of its consolidation by posttraining inhibition of protein synthesis, which blocks induction of learning-related synaptic plasticity. Finally, we have succeeded in transferring components of LTM from trained to untrained animals by injecting RNA from trained animals into naïve

ones. This apparent transfer of LTM can be blocked by inhibiting DNA methylation. Our results challenge the SPM hypothesis and point to changes within the nuclei of neurons as the mechanism of memory storage. SUPPORT: NINDS, NIMH, NSF

Gonzalez ST, Marty V, Lele S, Vo R, Yenokian I, Yang CQ, Ahmed K, Spigelman I, Fanselow MS (*Department of Psychology, University of California, Los Angeles*) Influences of stress severity and sex on changes in fear learning, anxiety and alcohol consumption following stress exposure ABSTRACT: Posttraumatic stress disorder (PTSD) develops after exposure to traumatic events and can involve an exaggerated fear response to stimuli that are reminiscent of the original stressor. In addition, PTSD is frequently co-morbid with other disorders including substance abuse. However, not all individuals who experience trauma develop PTSD and the factors that promote susceptibility versus resilience to the effects of stress are poorly understood, although the disorder occurs more commonly in women than in men. To understand these aspects of the disorder our laboratory has developed a model of stress exposure termed stress-enhanced fear learning (SEFL) that captures many of these features. In this model, exposure to a traumatic stressor (either 4 or 15 unsignalled footshocks) in one context sensitizes fear learning to a mild stressor (1 unsignalled footshock) in a second context. In this study we investigated the extent to which the SEFL model captures the heterogeneity of PTSD and identified potential predictors of susceptibility versus resilience to the effects of stress. In this study both male and female rats received assessments of anxiety and alcohol consumption prior to traumatic stress exposure, and a battery of fear learning, anxiety and alcohol consumption tests following stress exposure. We found that while males and females did not differ on most measures of fear learning following stress, males showed elevated anxiety relative to females. In addition, we found evidence of distinct "susceptible" and "resilient" populations that showed a constellation of behavioral changes relating to fear learning and anxiety. Lastly, we found that baseline levels of anxiety were uniquely predictive of susceptibility to the effects of stress in females, but not in males. These results indicate that the SEFL model is a powerful tool for probing the behavioral and biological factors that promote susceptibility versus resilience to the effects of stress.

Gonzalez Magana D, Furtak SC (*California State University of Sacramento*) Post-conditioning lesions of the perirhinal cortex impairs retrieval of the fear memory to a discontinuous conditioned stimulus. ABSTRACT: Recent studies have implicated the perirhinal cortex (PER) in fear learning under specific conditionings. In particular, the PER may become involved in fear learning when a conditioned stimulus (CS) requires its components to be unitized across time or modalities into a single representation, such as when the CS is discontinuous in nature. While several studies have examined perirhinal function during fear acquisition, few studies have assessed the PER involvement in fear extinction. Here, the involvement of the PER during fear extinction to a discontinuous CS was evaluated by damaging the PER two days after fear acquisition, which was prior to extinction training. During fear acquisition, rats received 5 pairings of a foot shock unconditioned stimulus (US) and a discontinuous light CS. Two days later, rats underwent surgery where animals either had an excitotoxin (Experimental group) or saline (Control group) injected into the PER. After 5-7 days of recovery, rats underwent fear extinction training, receiving 20 CS alone trials in the conditioning context. The next day rats returned to the conditioning context and received an addition 15 CS alone trials to test retrieval of the fear extinction memory. Results showed a significant decrease in freezing levels in the Experimental group compared with the Control group during both the extinction training and extinction retrieval test sessions. These results suggest the role of PER in stimulus unitization may extend beyond fear acquisition. SUPPORT: Supported by NSF 1755111 to S.C.F

Gostolupce D, Lay BPP, Iordanova MD (*Concordia University*) Bidirectional regulation of fear inference in the orbitofrontal cortex ABSTRACT: Animals can make inferences about events in their environment by linking memories forward and backward in time. For example, in sensory preconditioning (SPC) two cues (i.e. light and tone) are paired together before one of those cues (e.g. tone) is then paired with a shock. Subsequent presentation of the cue that was never directly paired with the shock (i.e. light) results in fear responses (freezing). That is, fear acquired to the tone is inferred retrospectively to the light. Another way to make similar inferences is second-order conditioning (SOC). In SOC, tone is paired with shock prior to pairings with the light. Again, subsequent presentations of the light evoke fear. This time, fear is inferred prospectively to the light. The only difference between these two procedures is the order of the training phases (SPC: tone–>shock after light–>tone; SOC: tone–>shock before light–>tone). The OFC has been implicated in retrospective reward inference. Here we used SPC and SOC to examine the role of the OFC in retrospective and prospective fear inference. Inactivation of ventrolateral OFC prior to test disrupted retrospective but enhanced prospective inference evident by attenuation in fear (freezing) to the sensory preconditioned cue but enhanced fear to the second-order cue. These data are considered in terms of the content of learning that controls behavior.

Gould TJ, Bangasser DA, Holliday ED (*Penn State and Temple University*) Adolescent stress and nicotine interact to disrupt adult hippocampal-dependent learning and stress response ABSTRACT: Adolescence is a developmental period associated with increased vulnerability to stress and for tobacco addiction. Nicotine exposure during this period leads to long-term changes in behavior and neural function. The present study examined the interactive effects of a brief exposure to shipping stress or experimentally-induced stress and chronic exposure to nicotine (12.6 mg/kg/day for 12 days) during adolescence on 1) cognitive function and stress reactivity in adulthood and 2) levels of corticosterone (CORT) in blood and expression level of glucocorticoid (GR) and corticotropin-releasing factor (CRFR) receptors in hippocampus during adolescence and adulthood. Adolescent (P31), but not young adult (P47), mice had higher levels of corticosterone after arrival at the facility compared to mice bred onsite. When mice shipped and bred onsite were given nicotine for 12 days beginning at P23 (pre-adolescent), P38 (adolescent), and P54 (adult) and then tested for conditioned fear learning 30 days later, the shipped mice, but not those bred onsite, exposed to nicotine as adolescents showed deficits in fear learning. Further-

more, adolescent mice bred in-house and exposed to acute laboratory induced stress and administered 12 days chronic nicotine starting 7 days after stress had deficits in adult contextual fear conditioning. No deficits were seen in cued fear conditioning, which suggests changes in hippocampal function as contextual but not cued fear conditioning is dependent on the hippocampus. Along with the learning deficit, adult mice who had been stressed and exposed to nicotine during adolescence showed increased expression levels of GR and CRFR in hippocampus as well as blunted CORT release in response to restraint stress even though there was no difference in baseline CORT 30 days after nicotine withdrawal. These results suggest that the developing adolescent brain is particularly sensitive to the detrimental effects of stress and nicotine. Importantly, studies examining adolescent behavior may need to consider whether mice are shipped or bred in-house SUPPORT: National Institute on Drug Abuse DA017949) and the Jean Phillips Shibley Endowment

Haskell AM, Servatius L, Handy JD, Wright WG, Servatius RJ. (*Syracuse VA Medical Center, Syracuse NY; Department of Psychiatry, Upstate Medical University, Syracuse, NY; Temple University, Philadelphia, PA*) Lifetime Experience of mTBI Blocks Facilitated Acquisition of Eyeblink Conditioning in Anxiety-Prone Veterans ABSTRACT: Military service and training increase risk of experiencing head injuries consistent with mild traumatic brain injury (mTBI). These head injuries could potentially exacerbate stress-related mental health difficulties such as posttraumatic stress disorder (PTSD). In previous work with active duty Service Members and Veterans, enhanced eyeblink conditioning was observed in those expressing current PTSD symptoms, with similar performance patterns apparent in those classified as behaviorally inhibited (BI). The current study examines eyeblink conditioning in veterans assessed for lifetime mTBI, PTSD symptoms and BI temperament. Eyeblink conditioning was assessed in Veterans (n = 40) using a partial reinforcement schedule in which a 500-ms tone conditioned stimulus (CS) co-terminated with a 50-ms air puff unconditioned stimulus (US) on 50% of trials; for the remaining 50% of trials, Veterans were exposed to the CS alone. Eyeblink conditioning was administered in two sessions separated by one week. For Session 1, Veterans completed 60 conditioning trials whereas 30 trials were used in Session 2. Based on AMBI and mTBI screens four groups were formed: non-inhibited, non-injured (NI-NI; n = 6), behaviorally inhibited, non-injured (BI-NI; n = 12), non-inhibited, injured (NI-mTBI; n = 14), and behaviorally inhibited, injured (BI-mTBI; n = 8) Veterans. As anticipated, BI was associated with higher total scores on the PCL-5 ($t(38) = 2.49$, $p = .017$), indicating higher incidence of PTSD symptomology in these Veterans. Consistent with previous eyeblink conditioning studies, BI Veterans exhibited facilitated acquisition of the eyeblink response compared to NI Veterans during Session 1 ($F(1, 36) = 4.34$, $p = .04$, $\eta p^2 = .11$). However this relationship was moderated by previous history of mTBI, such that BI-mTBI Veterans failed to demonstrate an appreciable learning advantage over NI-NI and NI-mTBI Veterans ($F(1, 36) = 8.17$, $p = .007$, $\eta p^2 = .19$). This pattern of performance was also present in Session 2; that is, positive learning biases in BI Veterans were moderated by the presence of previous mTBI ($F(1, 36) = 5.92$, $p = .02$, $\eta p^2 = .14$). Eyeblink classical conditioning shows promise as a means of objectively distinguishing mTBI from anxiety, and given the stability of behavioral performance over multiple sessions in the current study, may also serve as a means of tracking symptom resolution over time.

Herbst MR, LaViola M, Twining RC, Gilmartin MR (*Marquette University*) Prefrontal neuronal encoding of threat-related stimuli across the estrous cycle. ABSTRACT: The association of a neutral conditional stimulus (CS) and aversive footshock unconditional stimulus (UCS) that are separated in time, as in trace fear conditioning, requires activity in the prelimbic area (PL) of the medial prefrontal cortex. We have previously shown that a subset of PL cells shows sustained firing in response to the CS and that optogenetic silencing of prefrontal activity during the trace interval between the cue and shock prevents learning (Gilmartin & McEchron, 2005; Gilmartin et al., 2013). Recently, we have uncovered sex differences in the prefrontal cortical contribution to trace conditioning (Kirry et al., 2018; 2019). In one study, the estrous cycle gated the memory-impairing effects of a muscarinic antagonist in the PL (Kirry et al., 2019), which suggested that circulating ovarian hormones may modulate prefrontal encoding during aversive learning. Here we recorded neuronal activity in the medial prefrontal cortex during the acquisition and extinction of trace fear conditioning. The estrous cycle of female Long-Evans rats was tracked for two cycles and then half of the rats started training on the day of proestrus and the other half started training on the day of metestrus. Training occurred over two days and testing in a shifted context occurred when the rats returned to their initial training cycle stage. Initial results (n = 6/group) have revealed similar sustained activation to the CS but divergent encoding of the UCS during day 1 of training. Proestrus females exhibited a robust increase in firing in response to the UCS, and metestrus females exhibited a modest response. Neuronal encoding on day 2 of training and subsequent conditional fear to the cue and context at test was similar between groups. Follow-up experiments will determine whether these divergent patterns of PL encoding of the UCS mediate cycle differences in cued fear retention after only one day of training, that can be overcome with additional training. These findings will reveal how prefrontal encoding of threat-related stimuli does and does not change across the estrous cycle, shedding light on how neuromodulation of prefrontal activity differentially affects the formation of fear memories between sexes and across the estrous cycle. SUPPORT: This work is supported by the Whitehall Foundation Research Grant 2014-08-67, the National Science Foundation IOS:1558121, and the Charles E. Kubly Mental Health Research Center.

Heroux NA, Horgan CJ, Pinizzotto CC, Rosen JB, Stanton ME (*Department of Psychological and Brain Sciences, University of Delaware*) Inactivation of the medial prefrontal cortex or ventral hippocampus disrupts incidental context memory and regional immediate early gene expression in adolescent rats ABSTRACT: The Context Preexposure Facilitation Effect (CPFE) is a contextual fear conditioning paradigm in which acquiring a context representation, acquiring the context-shock association, and retrieval/expression of contextual fear occur in three distinct phases across three days. The medial prefrontal cortex (mPFC), dorsal hippocampus (dHPC), and ventral hippocampus (vHPC) are required for the acquisition and/or consolidation of a context representation during context preexposure in the CPFE (Heroux et al., 2017; Robinson-Drummer et al.,

2016; Rudy & Matus-Amat et al., 2005). The purpose of the current study was to examine whether mPFC or vHPC inactivation during context learning impairs the CPFE and interferes with hippocampal or other regional immediate early gene (IEG) activity induced by context exposure. Adolescent (Postnatal Day 31) Long-Evans rats were given intra-mPFC or intra-vHPC infusions of the GABAA receptor agonist muscimol or saline prior to context preexposure, and then were sacrificed 30min later and IEG mRNA expression (c-Fos, Arc, Egr-1, Npas4) was analyzed from dissected mPFC, dHPC, vHPC, and ventral midline thalamus (VMT) tissue. Inactivation of either structure during context exposure abolished both post-shock and 24hr retention test freezing in the CPFE. Prefrontal inactivation disrupted IEG expression in the mPFC, VMT, and VHPC, whereas ventral hippocampal inactivation disrupted mPFC, vHPC, and dHPC IEG expression during context learning. These results suggest that context memory processes on the preexposure day of the CPFE are likely supported by extended mPFC-vHPC circuitry not typically emphasized in configural learning and memory. Testing this potential interaction via pathway-specific excitation and inhibition across multiple stages of development remains a fruitful direction for future research. SUPPORT: NIH grant F31AA026503 to NAH; UNIDEL grant to MES

Hilz EN, Monfils, MH, Lee, HJ (*University of Teas at Austin*) Individual differences in response to amphetamine among female rats. ABSTRACT: Cue-directed behavior such as sign-tracking is thought to indicate enhanced motivational processing of CS information and has been shown to predict drug-seeking behavior (Flagel et al., 2007; 2011). Females are considered to be at increased risk for drug addiction and the gonadal hormone estradiol plays a particularly important role in female drug seeking behavior due in part to its up-regulatory relationship with dopamine. We recently investigated the viability of conditioned orienting (OR; a form of cue-directed behavior) as a potential phenotype which predicts drug-proclivity in female rats (Hilz et al., 2019). Female rats which express the OR phenotype (termed, 'Orienters') are shown to be more consistent in drug-seeking behavior in an amphetamine conditioned place preference (CPP) paradigm compared to females which do not express the OR phenotype (termed, 'Nonorienters'). Nonorienters extinguished preference to an amphetamine-associated context over 3 days while Orienters did not. Moving forward, the current experiment attempts to examine the neuromechanism responsible for individual differences in amphetamine CPP extinction. As a first step, we will examine the response of orexin cells (via FOS labeling) to either single or multiple exposures of amphetamine given the role of orexin in OR behavior (Wheeler et al., 2014), appetitive extinction (Keefer et al., 2016), and drug-seeking (Aston-Jones, 2010). Preliminary results suggest that OR phenotype does not influence FOS+ORX expression in the lateral hypothalamus after a one-time amphetamine exposure; results of multiple-exposures in response to amphetamine will be forthcoming. SUPPORT: Waggoner Center for Alcohol & Addiction Research

Hoffman AN, Watson S, Makridis A, Patel A, Giza CC, Fanselow MS (*Department of Psychology UCLA; Staglin Center for Brain and Behavioral Health at UCLA; Brain Injury Research Center at UCLA; Steve Tisch BrainSPORT Program*) Increased phonophobia and contextual fear in female rats following traumatic brain injury ABSTRACT: Traumatic brain injury (TBI) is a significant predictor for post traumatic stress disorder (PTSD). Prevalence of TBI is higher in males than females. However, females are 2-4 times more likely to have PTSD. Sex differences in stress reactions and learning and memory may underlie differences in psychiatric comorbidities that emerge following TBI. We have shown that auditory white noise is noxious to male rats following fluid percussion injury (FPI) and increases fear learning when used in auditory fear conditioning, but it is unclear whether females exhibit a similar PTSD-like phenotype. Adult female and male rats received either lateral FPI or sham surgery and 48h later received behavioral training. In this study, we first investigated sex differences in behavioral responses to white noise and noise-shock fear conditioning and contextual recent and remote fear memory. Groups were pre-exposed to white noise (75dB) the day before noise-shock fear conditioning to the same stimulus. FPI groups exhibited defensive behavior to white noise, which was significantly more robust in females, suggesting FPI increased auditory sensitivity. After auditory fear conditioning, females overall had reduced recent and remote contextual fear. We then looked at unsignaled conditioning to determine whether FPI affects contextual fear differently in males and females following FPI. To strong (0.9mA) or weak (0.5mA) shocks, FPI groups froze more following the first shock trial than sham and FPI groups also showed greater context fear, driven by the females in both shock conditions. Given that in general females display reduced contextual fear compared to males, our data suggest that females may be more affected by TBI as evidenced by greater phonophobia and context fear after FPI. These data demonstrate sex differences in emergent anxiety phenotypes following TBI that may contribute to comorbid PTSD.

Iordanova M, Esber, Deroche, Schoenbaum (*Concordia University; Brooklyn College, National Institute on Drug Abuse*) Conditioned Inhibition in the orbitofrontal cortex ABSTRACT: The orbitofrontal cortex (OFC) has a long-standing role in tracking and using reward expectations in a flexible manner to guide behaviour. It remain unknown, however, whether the OFC also processes cues that explicitly signal that an expected reward will not be delivered.. Using a conditioned inhibition design along with single-cell electrophysiology and machine learning algorithms, we provide evidence that OFC neurons classify compounds that contain an excitor and an inhibitor differently to a compound that contains an excitor and a neutral cue, an excitor alone, an inhibitor alone or a neural cue alone. Decoding analyses support this by showing that our classifier correctly decodes compounds that contain inhibitors as distinct from other compounds, yet inhibitors on their own are not distinct from neutral cues. These data provide novel evidence that the OFC processes conditioned inhibitors but only does this in the context of reward expectation.

Krueger JN, Wilmot JH, Puhger KR, Taratani-Ota Y, Nemes SE, Wiltgen BJ (*University of California, Davis*) Memory retrieval for context fear is disrupted by widespread increases, but not decreases in hippocampal activity ABSTRACT: It is well-established that the hippocampus plays an essential role in memory formation, consolidation and retrieval. Previous studies demon-

strated that dorsal hippocampal lesions or pharmacological inactivation following learning led to profound deficits in memory retrieval. The goal of the current study was to use cell-type specific promoters to excite or inhibit the dorsal hippocampus during context fear memory retrieval using optogenetics or chemogenetics. We found that inhibiting pyramidal neurons in CA1 of the dorsal hippocampus is largely ineffective at producing deficits in memory retrieval. Excitation of pyramidal neurons in this same region, in contrast, leads to profound and reliable amnesia. We also report that some silencing tools impair retrieval through paradoxical increases in dorsal hippocampus activity, most likely driven by disinhibition. Therefore, unlike previous lesion and pharmacological studies, our data suggest that context fear memories can be retrieved under widespread dorsal hippocampus silencing. However, expression of these memories is disrupted when the dorsal hippocampus becomes hyperactive during retrieval. The implication of these results for context fear conditioning models and the design/interpretation of optogenetic/chemogenetic behavioral experiments are profound.

Kryklywy JK, Anderson AK (*University of British Columbia; Cornell University*) Neural representations of hedonic touch ABSTRACT: The development of affective associations in Pavlovian learning inherently involves experiencing the pre-existing hedonic value of the unconditioned stimulus (US). For proximal senses such as taste or touch, hedonic information may be a central component of sensory coding. Interestingly, extraction of hedonic information is not performed by exclusively, or initially, our central nervous system, but is instead coded from the sensory receptor, at moment of contact. In the cutaneous system specifically, affective content is carried along distinct umylenated nerve fibres for both pain and pleasurable sensation, distinct from the mylenated nerve fibres carrying discriminative tactile information. While processing of discriminative tactile experience is known to occur in primary somatosensory cortices, recent work has suggested that the hedonic labeled lines may bypass these regions. The current study uses the analytic technique of representational similarity analysis (RSA) on distributed brain activity patterns to determine how tactile information is instantiated in human sensory cortices, as well as frontotemporal areas involved in interoception and affective experience. We determined that, though tactile information is valence coded at the onset, primary sensory cortices represent little to no hedonic information. In contrast, representative signatures of hedonic information were identified across frontotemporal regions. The relative strength and nature of information carried varies region to region: ventromedial prefrontal cortex represented multiple hedonic states independently, insula and anterior temporal cortex were biased towards negative hedonic information, while amygdala coded processed hedonic information. Overall, this suggests that tactile hedonic information coded by our peripheral nervous system bypasses traditional somatosensory areas, and is instead represented in regions more commonly associated with affective processing and interoception.

Lattal M (*Oregon Health & Science University*) Persistent effects of stress on reward-related behaviors ABSTRACT: A common finding from rodent studies of drug abuse is that acute or chronic stress can reinstate drug-seeking behavior after extinction. In most of these studies, the stressor occurs during the reinstatement test; very little is known about the effects on drug-seeking behaviors long after the stressor has occurred. We have adapted the stress-enhanced fear learning (SEFL) procedure to examine these persistent effects. I will review the rationale for using SEFL-based approaches for studying persistent effects of stress on reward-related behaviors. I will describe work from our laboratory showing that (1) the basic SEFL effect persists across both time (>30 days) and contexts (including contexts with an extensive association with methamphetamine or alcohol), (2) massive shock exposure persistently alters different aspects of reward-related behaviors, including response generalization and cue-induced reinstatement, and (3) that these persistent effects can be modulated by basolateral amygdala inactivation and by extinction in the original shocked context. These findings suggest that massive fear conditioning at Time 1 has multiple consequences on fear and drug-related behaviors at Time 2, even when the interval between Time 1 and Time 2 is on the order of weeks to months. I will discuss implications of these findings for current ideas about the relation between acute stress, PTSD, and drugs of abuse. SUPPORT: NIDA R01 025922, NIDA R01 047981, DOD W81XWH-14-2-0143

Laughlin L, Moloney D, Sears R, Cain C (*NYU School of Medicine, Nathan Kline Institute*) Reducing shock imminence, but not certainty, greatly improves active avoidance conditioning ABSTRACT: In the active avoidance paradigm, rats learn to suppress Pavlovian reactions (e.g. freezing) and emit instrumental actions (e.g. shuttling) to escape threats and prevent pain. Though most rats acquire the avoidance response (AR) within 150 trials, approximately 25% of animals exhibit high freezing and never master the task ("poor avoiders"). This has led some researchers and theoreticians to suggest that avoidance could not have evolved as a major mechanism of defensive learning, since unsuccessful encounters with a predator lead to death. We hypothesize that instrumental AR learning is recruited for coping with anxiety-inducing threats that signal distant or uncertain harm, rather than fear-inducing threats that signal imminent or certain harm. To test this, we modified the standard avoidance protocol in which the 15-second warning signal resulted in foot shock on 100% of trials when the AR is not performed. In experiment 1 (Contingency), the 15-second noise was used, but shocks were delivered on 100%, 50% or 25% of failed trials. In Experiment 2 (Imminence), noise always signaled foot shock, but the noise duration was varied (15, 60, 120 or 240 seconds). Reducing noise-shock contingency did not improve AR learning, but reducing shock imminence led to perfect avoidance for all rats in less than 45 trials (240s condition). Subsequent analyses confirmed that low-imminence ARs are instrumental and emitted with short latencies, comparable to high-imminence ARs in good avoiders. These results suggest that AR learning mechanisms evolved to cope with anxiety-inducing, rather than fear-inducing, threats. Reducing US imminence may have improved AR learning more than reducing US certainty because this condition triggers fewer incompatible Pavlovian fear reactions (i.e. freezing) without degrading the established relationship between the AR and US-omission. This protocol also solves a longstanding problem for active avoidance research by eliminating poor avoidance, thus enabling future studies of AR acquisition that require pre-training manipulations.

Lay BPP, Iordanova MD (*Center for Studies in Behavioural Neurobiology, Department of Psychology, Concordia University, Montreal, QC, Canada*) Distinct neuronal ensembles within the central nucleus of the amygdala regulate extinction learning. ABSTRACT: Correlational data from histochemical and physiological studies suggest that the central nucleus of the amygdala (CeA) is involved in learning when expected events are omitted. Attempts at delineating the causal contribution of CeA neurons to this learning have targeted the entire nucleus indiscriminately, disrupting the function of neurons. Recent research using selective approaches have uncovered that not all neurons within a brain area are recruited during learning. Rather, a specific neuronal ensemble supports learning with distinct subsets of neurons likely having different functional roles. We sought to determine the functional role of CeA neurons that have been explicitly activated by the omission of an expected reward. Fos is a widely used marker for neuronal activity and here, we used the Daun02 inactivation procedure to assess the causal role of activated c-fos-expressing CeA neurons in updating reward expectations during extinction. In the present study, male c-fos-lacZ transgenic rats were trained to expect the delivery of a food reward upon the presentation of an auditory cue. Subsequently, rats received non-reinforced exposure to the reward-associated cue to generate conditions of reward omission, that is extinction, and examine the effect of this on learning. Cell inactivation with Daun02 took place ninety minutes following the start of the non-reinforced session, presumably when the neurons that detected the reward omission were activated and the corresponding c-fos levels were at peak. This led to disruption in behaviour indicative of impaired retrieval of the extinction memory compared to rats that received a vehicle infusion, which left those neurons intact. Additional data show that further extinction learning was retarded in the absence of the neuronal ensemble in the CeA. Moreover, inactivating these extinction-responsive CeA neurons resulted in greater spontaneous recovery and reinstatement. Lastly, this disruption in behaviour was not due to drug diffusion into the basolateral amygdala.

Lay BPP, Pitaru A, Boulianne N, Iordanova MD (*Center for Studies in Behavioural Neurobiology, Department of Psychology, Concordia University, Montreal, QC, Canada*) Distinct neural substrates modulate fear overexpectation and extinction learning. ABSTRACT: The ability to alter previously established behaviour is key for survival. Two ways in which reductions in previously established conditioned behaviour can be achieved is through overexpectation and extinction. The infralimbic (IL) cortex and the orbitofrontal cortex (OFC) have been implicated in learning when expectations are adjusted downward. However, it remains unclear whether these two structures have a similar or dissociable role when expectations are reduced. Further, while the IL cortex has been implicated in fear extinction, the role of the OFC in fear is largely unknown. Using overexpectation and extinction of learned fear associations, we sought to examine the effect of the lateral OFC and IL cortex on the reduction of outcome expectancy and the resultant change in behavioural responding. Our findings reveal a double dissociation between these neural substrates in fear overexpectation and extinction learning. Specifically, we show that silencing the lateral OFC but not IL cortex prior to compound training in overexpectation disrupts the reduction in responding seen on test. Yet, inactivating the IL cortex but not lateral OFC prior to extinction training impairs within-session extinction as well as the retrieval of that extinction on test drug-free. These findings demonstrate that despite driving a reduction in behaviour in a theoretically similar manner, overexpectation and extinction learning can be dissociated at a neural level.

Lensing A, Boerger R, Zimmerman S, Wu J, Pickens C (*Kansas State University*) Adolescent/early adult alcohol consumption causes faster omission contingency learning, with the level of consumption correlated with parvalbumin-expressing neurons in the anterior cingulate cortex. ABSTRACT: We previously found that Long-Evans rats given chronic intermittent access (CIA) to alcohol during adolescence/early adulthood exhibit faster omission contingency learning compared to alcohol naÃŕve rats. Here, we aimed to replicate this finding and identify a potential neurobiological basis. Rats received CIA (n=12) or water-only (n=12) access for 6 weeks (PND 26-66). Ten days after completion of the CIA paradigm, rats began six sessions of autoshaping training in which presentation of two levers each predicted free delivery of reward. Over the following six sessions, rats underwent omission contingency testing, in which a reward was withheld if a subject made a response on one of the levers, while the other lever continued to predict free reward regardless of responding. We analyzed the omission data using two measures of responding: 1) whether a rat made at least one lever response on each trial and 2) the number of lever responses on each trial. In the trials with a response measure, we found a marginally significant effect of alcohol vs. water (Group X Lever X Training Day interaction). In the responses/trial measure, we found a significant effect of alcohol vs. water (Group X Lever X Training Day interaction), which indicated that the rats with prior alcohol access decreased their responses/trial on the omission lever faster than the alcohol naÃŕve group. Our results replicate our previous finding that adolescent/early adult alcohol consumption can have long-term effects that allow for faster omission learning. We also found evidence for a correlation between parvalbumin-expressing neurons in the anterior cingulate cortex and amount of alcohol consumed within the alcohol access group, however there was not a group difference between CIA and alcohol naÃŕve rats. Our results suggest that alterations in parvalbumin-positive neurons in anterior cingulate cortex are not responsible for our faster omission learning in the alcohol access group, but may represent individual differences that relate to other behavioral traits. Our future research will examine parvalbumin-expressing neurons in other brain areas, as well as other neurobiological markers, to determine the neurological basis of effects of alcohol access on omission learning.

Maes EJP, Sharpe MJ, Gardner MP, Chang C, Schoenbaum G, Iordanova MD (*Concordia Univ., Montreal, QC, Canada; Psychology, UCLA, Los Angeles, CA; Cell. Neurobio. Res. Br., NIDA IRP, Baltimore, MD*) Causal evidence supporting the proposal that dopamine transients function as a temporal difference prediction error ABSTRACT: Correlational and causal studies have shown that reward-evoked dopamine (DA) signals in the VTA function as re-

ward prediction errors (RPE). A critical component to this signal, according to temporal-difference (TD) learning, is the backpropagating of the error signal to the earliest possible predictor. That is, the DA response migrates back to the cue that predicts reward. It remains unknown, however, whether this cue-evoked DA response carries information regarding outcome expectation (prediction) or is a prediction-error. Here we sought to address this question using two classical behavioural paradigms, second-order conditioning and blocking. Second-order conditioning involves pairings between a neutral cue and a previously conditioned reward-predictive cue such that the neutral cue becomes predictor for the reward. In blocking, a previously trained reward-predictive cue is presented in compound with a neutral cue and this compound is followed by reward. Learning about the relationship between the neutral cue and the reward is blocked in the presence of the good predictor. By examining the effect of DA inhibition during second-order conditioning, we are able to determine whether dopamine is critical for reinforcing learning about conditioned cues. By examining the effect of DA inhibition during the reward-predicting cue in blocking, we are able to determine the role of dopamine on regulating reward prediction. Our data show that optogenetic inhibition of dopamine transients at the start of reward-predicting cues prevents acquisition of second-order conditioning without affecting blocking. That is, shunting DA neuron activity at time of the reward-predicting cue prevented that cue from reinforcing learning about itself. While this result could be explained irrespective of whether we disrupted reward prediction or a reward prediction error signal, our blocking data are only consistent with the latter hypothesis. Shunting DA neuron activity at time of the reward-predicting cue during the second phase of blocking did not disrupt the blocking effect, suggesting that the cue-evoked DA signal does not carry information about reward prediction. These results provide causal evidence that cue-evoked dopamine signals function as temporal difference prediction errors.

Maren S (*Texas A&M University*) Prefrontal-thalamic pathways involved in emotional regulation ABSTRACT: The nucleus reuniens (RE) is a midline thalamic region that is an anatomical interface between the medial prefrontal cortex (mPFC) and the hippocampus (HPC). Previous work reveals a critical role for this structure forms of learning and memory that require coordinated activity between the mPFC and HPC, such as spatial working memory. Coordinated HPC and mPFC activity has also been suggested to be involved in emotional regulation, including the regulating the expression of conditioned fear memories. In particular, this circuit has shown to be involved in fear extinction, a form of learning in which animals learn to suppress conditioned fear responses, such as freezing behavior. Critically, extinction learning is context-dependent and is preferentially expressed in the extinction context; outside the extinction context, fear to an extinguished conditioned stimulus returns or renews. Here we hypothesize that RE may be an important hub by which the mPFC might and HPC interact to acquire context-dependent extinction memories to regulate the expression of conditioned fear. Consistent with this hypothesis, our results reveal that that the RE and its mPFC afferents are critical for the extinction of Pavlovian fear memories in rats. Pharmacological inactivation of the RE during extinction learning or retrieval increases freezing to an extinguished conditioned stimulus (CS), however renewal of extinguished fear to the CS outside the extinction context was unaffected. In the extinction context, c-fos expression and spike firing in RE neurons were increased by the extinguished CS when fear was suppressed. The role for the RE in suppressing extinguished fear requires the mPFC, insofar as pharmacogenetically silencing mPFC->RE projection neurons or mPFC terminals in the RE impairs the expression of extinction memory. These results reveal that mPFC-RE projections inhibit the expression of fear, a function that is essential for adaptive emotional regulation.

Markowitz SY, Santos A, Zhang S, Ghemitri N, Fanselow MS (*Psychology, University of California Los Angeles*) Influences of Variable Stimuli Used in Trauma and Mild Stressor Contexts on Enhanced Fear Response ABSTRACT: One characteristic of Post Traumatic Stress Disorder (PTSD) is an exaggerated fear response to a mild stressor following exposure to an extremely stressful event, or trauma. Our laboratory has developed a model of this feature of PTSD called Stress Enhance Fear Learning (SEFL). In this model, exposure to a significant stressor (15 unsignaled footshocks) in one context sensitizes learning of a fear response to a novel stimulus or context conditioned by a mild stressor, typically 1 footshock. Having footshock as the stressor and conditioning stimulus raises the question of whether or not the two stressors must be similar in some capacity in order to trigger the exaggerated response. However, there is also evidence that exposure to trauma sensitizes the amygdala to future aversive stimulus input. This may in turn modify thresholds for fear conditioning. In this study we investigated whether using other aversive stimuli for the traumatic stressor, such as white noise bursts, can produce the same enhanced fear response to a mild stressor. We also investigated whether the traumatic stressor and the mild stressor must be the same stimulus to cause the exaggerated fear response. In the first part of this study male and female rats were exposed to unsignaled noise bursts in both the traumatic stressor and mild stressor contexts. In the second part of this study, male and female rats exposed to footshock stressors in the trauma context were exposed either one noise burst, two noise bursts or one footshock in the mild stressor context. We found that using white noise as a traumatic stimulus was not sufficient to cause enhanced fear response in a mild stressor condition using the same stimulus. Additionally, we found that while animals in the one noise or two noise mild stressor groups showed enhanced fear response compared to controls. The inability for noise stressor to cause SEFL suggests that the intensity or severity of stress is a critical factor in producing SEFL. The ability for shock stress to enhance conditioning to noise US relative to unstressed controls indicates that the stressful stimuli and the conditioning stimuli (US) need not be the same. Consistent with Poulos et al.'s findings, these results indicate that prior stress can convert a mildly aversive stimulus that usually cannot support fear conditioning into one that does.

Marton TM, Hussain Shuler MG (*Johns Hopkins School of Medicine*) A behavioral paradigm tests if pursuit-based dilating-timestep TDRL explains temporal decision making ABSTRACT: Upon investigating how spending time across pursuits is evaluated by an atomizable temporal difference reinforcement learning algorithm (TDRL), we prove that memoryless TDRL evaluations systematically fail to optimize reward rate. This failure can be miti-

gated by representing each pursuit using a time-dilating state space, wherein the amount of time spent in a subsequent state increases by a precise proportion. TDRL applied to a time-dilating state space explains the diverse suboptimalities observed over decades of investigating how animals decide to spend time. In particular, this compromise between atomizable learning and reward rate optimization preserves optimal forgo behavior, creates a suboptimal bias toward sooner-smaller rewards in mutually exclusive choices, and leads to a suboptimal unwillingness to abandon pursuits midway. Thus, pursuit-based dilating-timestep TDRL provides 1) the first general mechanistically-descriptive explanation of temporal decision making, 2) a normative rationalization for the neural representation of time, and 3) support for the TDRL decision-making framework in the time domain. Temporal decision making can consequently be understood as a near-future-biased misestimation of opportunity cost and an overestimation of the remaining reward rate available midway into a pursuit. Pursuit-based dilating-timestep TDRL is further equivalent to representing the infinite future within a finite horizon time, and representing the time spent outside an option as requiring a smaller apparent time. We present a collection of behavioral tasks that can qualitatively and quantitatively validate the near-future bias in opportunity cost and the overestimation of remaining reward rate predicted by pursuit-based dilating-timestep TDRL.

McCarthy NA, PEeterson RC, Cook-Snyder DR, Miller DP, Servatius RJ (*Neuroscience, Carthage College, Kenosha, WI; Central New York Research Corporation, Syracuse, NY; Stress and Motivated Behavior Institute, Rutgers Biomedical and Health Sciences, Rutgers, NJ; Psychiatry, State University of New York Upstate Medical University, Syracuse, NY*) Potential role for central amygdala activation associated with avoidance learning in Wistar-Kiyoto rats. ABSTRACT: Behavioral inhibition is a personality temperament characterized by a tendency to avoid novel stimuli. Behaviorally inhibited people show increased vulnerability to anxiety and stress disorders. Wister-Kiyoto (WKY) rats display behavioral inhibition, attain signaled lever press avoidance at a higher rate, and are more resistant to extinction than control, Sprague Dawley (SD) rats. Thus, we have proposed that WKY rats are a model for anxiety and stress research. In previous research, we trained WKY and SD rats on either 100% tone-shock pairing or 50% tone-shock pairing in a signaled lever-press avoidance task. WKY rats in both the 100% and 50% contingency displayed the highest rate of avoidance learning, while SD rats in the 50% contingency failed to acquire avoidance learning. WKY rats appear to acquire avoidance based on the expectation of shock, whereas SD rats appear to acquire avoidance based on the presence of shock reinforcement. In the present study, we sought to determine areas of the brain that are associated with enhanced avoidance acquisition in behavioral inhibition by staining for Zif using immunohistochemistry. Zif is an immediate early gene that is correlated with synaptic plasticity of neurons. WKY and SD rats were run in either 50% or 100% tone-shock pairings for 3 days, and then stained for Zif expression. Preliminary results suggest that the central amygdala displays a positive correlation between the number of Zif positive neurons and the percent avoidance of the animal, with WKY rats in a 100% tone-shock pairing demonstrating the largest increases in Zif expression. Our results suggest that activation of the central amygdala may correlate with avoidance acquisition, and future studies in behavioral inhibited models may shed light on the acquisition of symptomology in anxiety and stress vulnerable individuals and suggest therapeutic targets.

McDiarmid TA[1], Belmadani M[2,3], Liang J, Meili F[1], Mathews EA[4], Mullen GP[4], Rand JB[4,5], Mizumoto K[6], Haas K[1], Pavlidis P[23], Rankin CH[1,7] ([1] *Djavad Mowafaghian Centre for Brain Health, University of British Columbia, 2211 Wesbrook Mall, Vancouver, British Columbia V6T 2B5, Canada;* [2] *Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, British Columbia V6T 2A1, Canada;* [3] *Michael Smith Laboratories, University of British Columbia, 2185 East Mall, Vancouver, British Columbia V6T 1Z4, Canada;* [4] *Genetic Models of Disease Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma 73104;* [5] *Oklahoma Center for Neuroscience, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73104;* [6]. *Department of Zoology, University of British Columbia, 2350 Health Sciences Mall, Vancouver, British Columbia V6T 1Z4, Canada;* [7]. *Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, British Columbia V6T 1Z4, Canada*) Systematic phenomics analysis of Autism-associated genes reveals parallel networks underlying reversible impairments in habituation ABSTRACT: A major challenge facing the genetics of Autism Spectrum Disorders (ASD) is the large and growing number of candidate risk genes and gene variants of unknown functional significance. Here, we used Caenorhabditis elegans to systematically functionally characterize ASD-associated genes in vivo. Using our custom machine vision system we quantified 26 phenotypes spanning morphology, locomotion, tactile sensitivity, and habituation learning in 87 strains each carrying a mutation in an ortholog of an ASD-associated gene. We identified hundreds of genotype-phenotype relationships ranging from severe developmental delays and uncoordinated movement to subtle deficits in sensory and learning behaviors. We clustered genes by similarity in phenomic profiles and used epistasis analysis to discover parallel networks centered on CHD8âĂćchd-7 and NLGN3âĂćnlg-1 that underlie mechanosensory hyper-responsivity and impaired habituation learning. We then leveraged our data for in vivo functional assays to gauge missense variant effect. Expression of wild-type NLG-1 in nlg-1 mutant C. elegans rescued their sensory and learning impairments. Testing the rescuing ability of conserved ASD-associated neuroligin variants revealed varied partial loss-of-function despite proper subcellular localization. Finally, we used CRISPR-Cas9 auxin inducible degradation to determine that phenotypic abnormalities caused by developmental loss of NLG-1 can be reversed by adult expression. This work charts the phenotypic landscape of ASD-associated genes, offers in vivo variant functional assays, and potential therapeutic targets for ASD. SUPPORT: This work was supported by a Canadian Institutes of Health Research Doctoral Research Award to TAM, Simons Foundation Autism Research Initiative (#205081) and Autism Speaks grants (#1975) to JBR, a SFARI award (#573845) to KH (PI), PP and CHR (co-PIs), and a Canadian Institutes of Health Research project grant (grant #CIHR MOP 130287) to CHR.

Meyer HC, Lee FS (*Weill Cornell Medicine*) A novel role for the ventral hippocampus in the conditioned inhibition of threat responding ABSTRACT: Threat responses facilitate self-preservation

by increasing vigilance and helping to avoid potential danger. However, difficulty regulating threat responses can interfere with goal-directed activities and is the hallmark of fear and anxiety disorders. Conventional behavioral treatments have limited long-term efficacy for a notable percentage of the patient population, particularly during development. This highlights a critical need to optimize interventions based on alternative neurobiological pathways for fear reduction. Using fiber photometry targeted to the ventral hippocampus, our lab has investigated the circuit-based mechanism by which explicit safety cues can be used to attenuate threat responding (i.e., conditioned inhibition). During a test session while mice were exposed to threat, safety, or a simultaneous "compound" presentation of both threat and safety cues, activity in target-defined (prelimbic, infralimbic or basolateral amygdala) ventral hippocampal subpopulations differed during the three cues. In addition, our findings highlight a novel role for prelimbic-projecting ventral hippocampal neurons in inhibiting threat responding in the presence of a safety cue. An additional experiment recording from prelimbic-projecting ventral hippocampal neurons in adolescent mice (postnatal day 35) indicated that generally increased activity in developing prelimbic-projecting neurons may provide a unique 'sensitive window' for the enhanced efficacy of safety cues to attenuate threat responses. Together, our findings highlight the potential to enhance intervention approaches for anxiety disorders, including those disorders emerging during adolescence, by targeting a novel neural mechanism through safety learning.

Miller, DP, Miller, JR, Cook-Snyder, DR, Allen, MT, Servatius, RJ, Martino, PF (*Carthage College, Kenosha, WI; Stress and Motivated Behavior Inst., Syracuse, NY*) Using enhanced CO2 to examine physiological differences in behaviorally inhibited females ABSTRACT: Behavioral inhibition (BI) is defined as a relatively stable temperamental tendency to avoid or withdraw from the unfamiliar (e.g., Kagan et al., 1987). The learning diathesis model suggests that individuals who are more vulnerable to anxiety disorders show enhanced associative plasticity to environmental relationships, which leads to symptom endurance and pathology. Recent reviews detailed numerous studies which have demonstrated that individuals with BI show enhanced and persistent learning (e.g., Allen et al., 2019). The tasks reviewed included avoidance learning and classical conditioning. However, these tasks rarely illicit any significant physiological response to the stimuli used. We hypothesized that, under significant physiological stress challenge, BI individuals would show differences in stress response. To that end, we administered enhanced CO2 (7%) for a 4 min period of time to female participants while they played a computer game. We tested whether respiratory stress response would be altered in BI individuals compared to non-inhibited individuals (NI; as determined by the AMBI, Gladstone and Parker, 2005). Participants used a Hans Rudolph mouth piece with nose occlusion. Each session began with 15 minutes of air to allow the participant to adjust to the breathing apparatus. During respiratory challenge, participants inhaled either 7% CO2 gas (room air balance) or room air. A recovery period followed where all participants inhaled room air. Participants receiving 7% CO2 showed rapid and consistent increases in all respiratory measures while breathing the gas, regardless of BI or NI categorization. However, BI participants showed reduced breathing frequency prior to the CO2 challenge compared to NI participants. They also showed reduced breathing frequency during the challenge period, regardless of whether they received CO2 or room air. During the recovery period, BI and NI participants showed similar breathing frequency. Krause and colleagues demonstrated in goats that stimulating the preBotzC of the medulla oblongata with 80% CO2 increased breathing frequency by 180% and disrupted airflow (Krause et al., 2009). Our data suggest that an area such as the preBotzC in BI females may be altered or that the signaling to or from the respiratory nucleus may be different than in NI females. Further, our data demonstrate that physiological stress response in BI individuals can be altered in comparison to NI individuals, a factor that may increase risk vulnerability for stress disorders.

Miller RR, Li A, Alcaide DM, Witnauer JE, Castiello De Obeso S, Murphy RA (*SUNY-Binghamton, SUNY-Brockport, University of Oxford*) Contrasting number of trials with duration of trials in contingency learning ABSTRACT: In a contingency learning situation, using a rapid-trial streaming procedure containing X-Y pairings (A trials), X-alone (B trials), Y-alone (C trials), and neither X nor Y (D trials), we independently varied, by the same fraction, the number and duration of each type of trial. Consistent with prior research, contingency ratings increased strongly with number of A trials, decreased moderately with number of B and C trials, and increased weakly with number of D trials. Across multiple experiments, a weak but significant effect of trial duration was also detected, which was always in the same direction as number of trials. For each type of trial, number of trials had a much larger effect size than did duration of trials. Thus, increasing the number of A, B, C, or D trials affected contingency ratings, even when A, B, C, or D trial durations, respectively, were proportionately reduced. These results were observed with both simultaneous and sequential presentations of X and Y. Critically, learning can be enhanced by providing more but shorter trials, thereby circumventing the cost of longer training sessions normally engendered by more trials or distributed practice. SUPPORT: NIMH

Miskovic V (*Binghamton University*) Aversive Learning in the Human Visual System ABSTRACT: Traditionally, the sensory cortices have been conceptualized as consisting of a hierarchical bank of low-level analyzers that encode, in a largely feed-forward and fixed manner, the physical dimensions of stimuli within a specific modality. The visual system, in this classical model, is understood to be an organized collection of spatio-temporal filters that are selective for luminance changes at particular orientations and scales, with increasingly complex representations at higher hierarchical levels. However, more recently, there has been a conceptual shift in characterizing the sensory cortices (including the earliest levels of the sensory hierarchy) in terms of flexible adaptive processor units rather than as simple analyzers registering veridical impressions. In other words, rather than being invariant and inflexible, the representational space of various sensory systems can be "tuned" or "warped" by learning and experience. In this talk I will review findings from our laboratory demonstrating the effects of aversive conditioning on the human visual cortex, combining evidence from cortical electrophysiology and psychophysics. Together, these studies provide greater insights into how the human visual system is able to adapt to recent learning histories, in order to facilitate responding

to learned threat and safety cues in one's environment.

Mohammadmirzaei N, Alicea Pauneto A, Knox D (*University of Delaware*) The effect of traumatic stress on Mu opioid receptor dynamics in brain regions associated with emotional learning and addiction. ABSTRACT: The onset of post-traumatic stress disorder (PTSD) often precedes and increases the risk for subsequent development of substance use disorder. Individuals with opioid dependence have the highest prevalence of PTSD (33%) compared with all other substance abuse. Hyperarousal and heightened anxiety are common symptoms of PTSD which are frequently addressed through opioidergic drug prescriptions. Opioidergic systems are also implicated in facilitating emotional reactivity, including the modulation of fear, the suppression of affective defense behavior, and anxiolysis. Since, endogenous opioids have inhibitory and modulatory roles in emotional responses, we hypothesized that Mu opioid receptor dysregulation in brain regions associated with emotional learning and memory may be particularly sensitive to the effects of traumatic stress. In order to test this hypothesis, we used the single prolonged stress (SPS) model of PTSD in rats. SPS is a procedure consisting of serial stressors (restraint, forced swim, and ether exposure) applied over a three-hour window which mimics the behavioral and neurological symptoms of PTSD. Rats were exposed to SPS or control stress, euthanized, and brain tissue were collected 7 days later. For the first set of rats, the medial prefrontal cortex (mPFC), amygdala and dorsal hippocampus, were dissected out of coronal brain sections. Then using western blot, the total Mu opioid receptor in these brain regions was assayed. For the second set of rats, mPFC, amygdala and dorsal hippocampus were dissected. And the cytosolic and membrane proteins from these brain regions were separated. We then assayed Mu opioid receptors in all samples using western blot. Since, there are other ways through which Mu opioid receptors can get deactivated (other than the internalization process), for the third set of rats, we used a cAMP assay to quantify and compare the amount of active Mu opioid receptors in the above brain regions in SPS and control groups. For the fourth set of rats, 30-50Âţm brain sections were taken from mPFC (IL, PL, Cg), nucleus accumbens (core and shell), amygdala (BLA and CeA), dorsal and ventral hippocampus (CA1, CA2, CA3), ventral tegmental area (VTA), and locus coeruleus (LC). We assayed the total Mu opioid receptor expression in these regions using immunohistochemistry. With regards to the effects the opioids have on the dopaminergic system and the importance of this system in emotional learning and addiction, we also examined the D1/D2 dopamine receptors in the above brain regions using near-infrared immunohistochemistry with high resolution scanning. The study is ongoing, but the preliminary data showed a decrease in total Mu opioid receptors of amygdala in the SPS group which suggests a down-regulation in the Mu opioid receptors. However, SPS had no effect on total Mu opioid receptor expression in the mPFC or dorsal hippocampus. Furthermore, cytosolic/membrane Mu opioid receptor ratios increased in mPFC, amygdala and dorsal hippocampus in SPS animals; a pattern of results indicative of changes in Mu opioid receptor internalization. The result of immunohistochemistry showed a decrease in Mu opioid receptor expression in the CA1 region of the dorsal hippocampus and LC and an increase in VTA of SPS rats in comparison to the control group. We did not see any changes in total Mu opioid receptors in all the other regions. Thus far, the preliminary data suggests that SPS exposure changes Mu opioid receptor function in the brain regions associated with emotional learning and addiction.

Mondello JE, Trott JM, Fanselow MS (*Department of Psychology, University of California, Los Angeles, CA, USA*) The effects of stress on morphine-induced conditioned place preference ABSTRACT: Stress and traumatic experiences are known to increase individuals' susceptibility to substance use disorders. Moreover, post-traumatic stress disorder (PTSD) is more likely to precede rather than follow development of substance use disorders. Given the high levels of co-morbidity between the two disorders, there is a great need to investigate common underlying mechanisms between the two. Stress enhanced fear learning (SEFL) is rodent model of stress exposure that captures aspects of PTSD, including the enhancement of subsequent associative fear learning. It is not known, however, if the stressor that produces SEFL can also impact other forms of learning, particularly reward learning. Conditioned place preference (CPP) is a behavioral procedure used to asses appetitive associative learning by pairing a context with drug administration. In this set of studies, we administered the stressor utilized in SEFL (15 footshocks administered pseudo-randomly across 90 minutes) and the subsequent day began morphine-induced CPP training. In the first study, adult male Long Evans rat received 4 pairings of both morphine (either 2.5 or 10mg/kg, s.c.) and saline in separate, distinct contexts. Training lasted 8 days with alternating pairings of morphine or saline each day. Following training, animals received three days of free access to the conditioning chamber to test for preference. Because expression of preference may differ depending on whether the drug is present or not, all animals were then tested following administration of their respective training dose of morphine. Preliminary findings suggested a trend for a stress by test day interaction, in that a history of stress may slow extinction. Given that 4 pairings of morphine resulted in very high levels of preference, possibly resulting in a ceiling effect, the subsequent study involved only 1 pairing of 2.5 mg/kg morphine (s.c.). One day post-training, animals were tested for preference in a drug-free state and the subsequent day they were tested again for preference following morphine administration (2.5 mg/kg, s.c.). On the first test day we found a trend for an impact of stress, in that stress enhanced preference for the morphine-paired context. Following morphine administration, we found that animals that had received the stressor showed a significant enhancement of this preference as compared to animals that had not received the stressor. Taken together, these results indicate that the stressor used for SEFL may not only enhance future fear associative learning but also future opioid-related reward learning. These findings also support the robust evidence that prior stress can enhance the rewarding properties of opioids, increasing individuals' risk for future substance use disorders.

Moscarello JM (*Texas A&M*) Fear, Anxiety, and Two-Way Signaled Active Avoidance ABSTRACT: A hallmark of two-way signaled active avoidance (SAA) in rat is that acquisition of the avoidance behavior (shuttling) leads to the suppression of fear elicited by the warning stimulus. Because the avoidance response becomes more robust as fear diminishes, this seemingly paradoxical transition makes it unclear what mediates SAA on a psychological level. Drawing from established theory (predatory imminence), I propose

that the gradual acquisition of the avoidance contingency causes the subject to encode an increase in the âĂŸpsychological distanceâĂŹ between the warning signal and the US (shock) as the density of shocks decreases and the time since the last shock increases. Thus, over the course of SAA training, the warning signal comes to produce an aversive state more consistent with anxiety (triggered by distal threats) than fear (triggered by imminent threats). In keeping with this hypothesis, I will present evidence that a key substrate for processing distal and uncertain threats, the bed nucleus of the stria terminalis (BNST), is necessary for the expression of the avoidance response and may function as a crucial node unifying a broad network of brain regions that have been demonstrated to underlie SAA (e.g. prefrontal cortex, nucleus accumbens). The psychological function of this circuit will be discussed in the context of avoidance and other conditioning paradigms that suppress cue-evoked fear (e.g. extinction), which recruit a comparable system of neural substrates.

Ng KH, Sangha S (*Department of Psychological Sciences, Purdue University., Purdue Institute for Integrative Neuroscience*) Learning-related changes in infralimbic cortical activity during conditioned inhibition of fear ABSTRACT: Expressing fear behavior in the absence of threat is maladaptive because it decreases the opportunity to seek life-sustaining substances. Learned safety signals can rescue an organism from this immobilizing state to resume exploratory behaviors. The infralimbic (IL) region of the prefrontal cortex is known to be critical for consolidating fear extinction and for suppressing fear in the presence of a safety cue. IL neurons have also been shown to increase activity to an extinguished fear cue during the recall of fear extinction. We thus hypothesized that IL neurons would also encode for safety signals that are actively suppressing fear behavior in a situation that may be perceived as potentially dangerous. We recorded from IL neurons using multi-array electrodes during a safety-fear-reward cue discrimination paradigm that is well established in our laboratory. We monitored multiunit activity to assess global changes in IL activity, and single-unit activity to assess changes in recruitment of individual neurons encoding for safety. During the discrimination task, rats learned that the reward cue resulted in sucrose delivery and the fear cue resulted in footshock, but when the fear cue was simultaneously presented with the safety cue as a compound cue (fear+safety cue), there was no footshock. To control for sensory modality effects, we also trained a separate group of animals with the modalities (auditory vs visual) counterbalanced for the fear and safety cues. Male rats showed high freezing to the fear cue and significantly lower freezing to the fear+safety cue, regardless if the safety cue was an auditory or visual cue. Our multi-unit data demonstrated increasing IL neuronal firing to the combined fear+safety cue across learning sessions, matching the magnitude of behavioral fear suppression to the fear+safety cue. This learning-related increase was not seen to the fear, safety or reward cues and did not depend on cue modality. These data suggest the IL is engaged when a behavioral fear response is being actively regulated during cues signifying safety.

Oleksiak CR, Ramanathan KR, Miles OW, Moscarello JM, Maren S (*Department of Psychological and Brain Sciences and Institute for Neuroscience, Texas A&M University*) Signaled Active Avoidance Performance is Context-Dependent ABSTRACT: After Pavlovian fear conditioning, the expression of conditioned fear is context-independent: rats that learn an association between a conditioned stimulus (CS) and an aversive unconditioned stimulus (US) in one context will show robust fear responses, such as freezing, to the CS in a different context. It is unclear whether other learned defensive responses, such as active avoidance behavior, are context-independent. Here we examined whether two-way signaled active avoidance behavior in rats is affected by a context shift. Sprague-Dawley rats received four days of signaled avoidance conditioning which consisted of thirty tone warning signals (2 kHz, 80 dB, 15 s) paired with footshock (0.7 mA, 0.5 s) per day. Rats could avoid the footshock US and terminate the warning signal by shuttling from one side of the apparatus to the other prior to US onset. After conditioning, the rats had two counterbalanced tests in either the conditioning context or in a shifted context. In both tests, 10 tones were presented absent shock and avoidance responses did not terminate the tone (i.e. both tests were 'reinforcement-free'). The rats performed significantly fewer avoidance responses in the shifted context compared to the original context. This was accompanied by an increase in freezing to the warning signal in the shifted context. Hence, unlike Pavlovian fear conditioning, active avoidance conditioning is context-dependent. Future work will examine the neural circuits mediating the context-dependence of avoidance responses.

Opara V, Mahmud A, Cossette M-P, Lay BPP, Iordanova MD (*Concordia University*) Mesolimbic dopamine regulates aversive prediction error ABSTRACT: Learning to predict events in our environment depends on prediction error, that is, the discrepancy between real and expected events. In the context of reward learning, prediction error is represented by the phasic dopamine (DA) signal in the VTA. Whether this signal has any role in learning about aversive events remains unclear. To investigate this, rats were trained in an aversive blocking paradigm. In blocking, the formation of an association between a target cue (e.g. clicker) signalling shock is blocked or impaired if this cue is presented in compound with another cue (e.g. light) that has been previously trained as a reliable predictor of the same shock. Using optogenetics, we bidirectionally manipulated the dopamine signal at time of an expected (or unexpected in the case of the controls) shock. Optogenetic activation of VTA DA neurons or their terminals in the NAc augmented, whereas optogenetic inhibition of VTA DA neurons attenuated the blocking effect. These data are critical in uncovering a role for the VTA DA signal in aversive prediction error and suggests that it regulates learning in a valence-specific manner.

Ortiz S, Halcomb C, Latsko M, Costanzo C, Beaver J, Dutta S, Adkins J, Jasnow A (*Kent State University*) Corticosterone administration after early adolescent stress selectively blocks stress-induced potentiation of morphine place preference in adulthood. ABSTRACT: Opioid use disorder (OUD) is a large public health concern within the United States. A significant predictor of the development of OUD is a pre-existing anxiety disorder, which may contribute to the high comorbidity between anxiety disorders and OUD. Another significant predictor of anxiety and substance abuse disorders in adulthood is childhood or adolescent trauma âĂŞ psychological or physical. Here we explore the longitudinal effects of

early adolescent stress, and the treatment thereof, on the rewarding properties of opioids in adulthood. Using various stressors on mice during early adolescence (PND 30-31), we test the effects of the stress on the rewarding properties of morphine in adulthood (PND 72). To assess morphine reward, we use morphine-induced conditioned place preference (CPP) paradigm in which the motivational properties of morphine are repeatedly paired with a neutral context, that can later elicit an approach behavior toward the morphine-paired context. The effects of stress during adolescence have a long-term effect on potentiating CPP into adulthood. However, no study, to our knowledge, has investigated the effects of treatment interventions post-adolescent stress to alleviate the detrimental effects of stress on both the memory of the stressor and the increased rewarding properties of drugs. A current treatment intervention after trauma in clinical populations is hydrocortisone, a steroid hormone which has shown to be successful at reducing PTSD symptoms three-months after the trauma exposure. We found that the rodent equivalent of hydrocortisone, corticosterone, administration after stress in adolescence selectively ameliorates the impact of the stressor and normalized morphine preference to levels comparable to non-stressed controls. These findings help to uncover potential treatments to aid in the prevention of addictive behaviors.

Pajser A, Fisher H, Pickens CL (*Kansas State University*) The role of mu-opioid receptors in conditioned fear learning in high vs. low alcohol drinking rats. ABSTRACT: PTSD and alcohol abuse frequently co-occur, but the cause of this co-morbidity is unclear. Alcohol exposure could alter problem drinkers' brains to promote the development of anxiety disorders, problem drinking could occur because of pre-existing anxiety (e.g.: self-medication), or a pre-existing factor could affect both anxiety and alcohol consumption. Previous research in our lab has found an association between the amount of alcohol a rat will voluntarily consume and their fear expression when tested in extinction, such that rats that consume higher levels of alcohol show lower levels of fear (both in limited and extended training fear conditioning). Because the opioid system can affect both alcohol consumption and fear learning, we chose to examine whether the individual differences in voluntary alcohol consumption and fear responding we have previously observed are due to individual differences in the opioid system. As an initial study, we investigated the role of the mu-opioid receptor system by administering naltrexone before fear conditioning sessions in high and low drinkers. Male Long-Evans rats received chronic intermittent alcohol access (CIA) or water-only access for 6 weeks (PND 26-66). We divided the rats (based on their drinking in early adulthood- the last 2 weeks of access) into high alcohol drinkers (consumed >2.5 g/kg/24-h alcohol), low alcohol drinkers (consumed <2.0 g/kg/24-h alcohol), or water drinkers (no alcohol access). Rats were then food-restricted and began behavioral training 9 days after the final alcohol access period, with fear conditioning taking place 15 days after the final alcohol access period. The rats were trained to lever-press and then received single day of fear conditioning. Half of the rats in each of the 3 drinking groups received a 1 mg/kg subcutaneous injection of naltrexone 10 minutes prior to a fear conditioning and the remaining rats received a saline injection at the same time. The rats were tested for conditioned fear (measured with conditioned suppression of lever-pressing) two days after the end of fear conditioning, with no pre-test injections. Naltrexone administration prior to fear conditioning increased fear expression in all three groups in the extinction test, with no interaction between drinking group and training injection. Our future studies will investigate the role of other components of the opioid system, such as the kappa- and delta- opioid receptors, using similar methods. SUPPORT: National Institute of General Medical Science GM113109 of the National Institutes of Health.

Palmer JL, Eck SR, Ardekani CS, Holley AM, Luz S, Salvatore M, Kim ED, Bhatnagar S, Bangasser DA (*Temple University, University of Maryland School of Medicine, Children's Hospital of Philadelphia*) Effects of early life adversity on steroid hormones and male sex behavior in rats ABSTRACT: Adversity early in life is a risk factor for later impairments in cognition, motivation, and stress responsivity. To model this adversity, our laboratory utilizes the limited bedding and nesting (LBN) manipulation in which rat dams and pups are housed in a limited-resource environment from postnatal days 2 through 9. LBN appears to shift dams into a hypervigilant state, where they engage in more pup-directed behaviors but fewer self-care behaviors than dams in a standard housing environment. Although the LBN manipulation is known to have lasting consequences on pup development, few studies have assessed changes in hormone exposure. We found that LBN male and female rats have shortened anogenital distances prior to puberty compared to sex-matched controls, which implies a decrease in early androgen exposure. Additionally, the manipulation increased plasma estradiol levels in adulthood. These data suggest that LBN has a demasculinizing effect in males, which could alter a range of behaviors, including sexual behavior, in adulthood. Ongoing studies are testing whether LBN leads to differences in mounts, intromissions, and ejaculations. Preliminary data show a trend for fewer ejaculations in LBN males compared to their control counterparts. While an increase in copulatory efficiency is typically anticipated with greater sexual experience, we hypothesize that this effect may be dampened in those rats that experienced LBN. We expect to confirm our initial findings with more subjects and to demonstrate impaired performance between groups over multiple sexual encounters. These data would suggest that one way by which LBN can have a lasting impact on behavior is via brain demasculinization.

Parkes SL (*CNRS, INCIA, Université de Bordeaux*) Cortical contributions to goal-directed behaviour in rats. ABSTRACT: Appropriate decision making is critical for adapting to a changing environment. Every day we must make decisions based on internal goals and the expectation that a given action will lead to goal achievement. Such decisions are experimentally defined as "goal-directed." Several regions of the mammalian cortex are involved in the integration of sensory, affective and cognitive information to guide flexible choice between competing actions. Current evidence indicates that, in the rat, these regions principally involve medial prefrontal, orbitofrontal, and insular cortices. Importantly, the emerging view is that each of these areas provides a distinct contribution to goal-directed behaviour. Cortical co-ordination may therefore prove essential to flexible action control. Here, I will review evidence from free operant tasks employing causal interventions to outline the distinct involvement of these cortices in goal-directed action.

Pickens CL, Ma X, Wu J (*Kansas State University*) The value of inter-trial interval reinforcers is based on absolute, rather than relative, length of the interval during nonreward ABSTRACT: Trial-based behavioral experiments in humans and non-human animals often have extended inter-trial intervals (ITI) after incorrect responses. However, it unclear whether longer ITIs have reinforcement or punishment value. Here we examined whether alterations in the ITI have value in motivating behavior in humans. Undergraduate students participated in a computer-based discrimination task with colored line stimuli presented on the screen. Participants could make or withhold a response to each of 4 line stimuli, followed by visual feedback (a smiley face) or a blank screen. The four stimuli were: Reinforced (smiley for a response), Non-reinforced (no smiley regardless of responding), Non-contingent reinforcement (smiley regardless of responding) and Omission contingencies (smiley presented if a response was withheld). There were four groups: The Low and High groups had a same length of post-stimulus interval regardless of whether a smiley or blank screen was presented (0.5 or 3.5 second in Low and High, respectively), so that responding had no effect on how soon the next trial began. The Advantage group had a 0.5-second smiley and a 3.5-second blank screen, so earning visual feedback made the next trial start faster. The Disadvantage group had a 3.5-second smiley and a 0.5-second blank screen, so earning visual feedback made the next trial start later. Reinforcement value was measured by responses to the Reinforced stimulus minus to the responses to the Non-reinforced stimulus (reinforcement difference score), and punishment value was measured by responses to the Non-contingent stimulus minus responses to the Omission stimulus (punishment difference score). We found main effects of Blank Screen length for both measures, with no effect or interaction of Visual Feedback Length. In both measures, longer Blank Screen length led to greater difference scores. Our results suggest that the ITI can be an important motivator of behavior in reinforcement and punishment, but the motivational power appeared to be based on the length of the blank screen outcome rather than the length of the visual feedback outcome. This motivational value appeared to be based on the absolute length of the blank screen rather than its length relative to the length of the visual feedback. Our future research will examine whether there are limits to this sensitivity to absolute (rather than relative) blank screen length as the interval becomes longer, and whether the motivational value in our task is related to individual differences in other traits.

Pinizzotto CC, Heroux NA, Horgan CJ, Stanton ME (*University of Delaware*) Role of dorsal hippocampal cholinergic activity in context-shock encoding during the Context Preexposure Facilitation Effect (CPFE) ABSTRACT: The Context Preexposure Facilitation Effect (CPFE) is a contextual fear conditioning paradigm that separates learning about the context (preexposure day), acquiring a context-shock association (training day), and retrieval/expression of this association (testing day) across three days. Acquisition is measured with a post-shock freezing test, while retrieval/expression is measured with a retention freezing test 24 hours later. Our lab has found that systemic injection or intra-dorsal-hippocampal (dHPC) infusion of the muscarinic receptor antagonist, scopolamine, prior to preexposure or immediate-shock training impairs retention freezing in the CPFE. The deficit caused by pre-training scopolamine may reflect impaired retrieval of the context representation, encoding of the context-shock association, and/or consolidation of the context-shock association (Robinson-Drummer et al, 2017). The current experiments replicated and extended these findings by examining the effects of systemic or intra-dHPC scopolamine administered prior to immediate-shock training on post-shock freezing in adolescent rats. Systemic or intra-dHPC infusions of scopolamine prior to training disrupted both post-shock and retention freezing to the level of non-associative controls. These results suggest that retention deficits caused by pre-training scopolamine reflect an impairment in the retrieval of a context representation and/or the acquisition of a context-shock association in the CPFE. Testing whether this role of hippocampal cholinergic activity changes across different contextual fear conditioning paradigms is an avenue for future research.

Pribic MR, Dybing K, Rose JK (*Western Washington University*) Associative conditioning of a glutamate-dependent locomotor response is modulated by simultaneous activation of GABAergic or cholinergic signaling in C. elegans ABSTRACT: It is well known that associative conditioning results from paired presentations of sensory stimuli resulting in a conditioned response (CR). In C. elegans, touch-sensitive mechanosensory neurons use glutamate to signal to command interneurons to drive forward or backward locomotion response networks. When a mechanosensory stimulus is repeatedly paired with a light stimulus (470 nm), subsequent responding to the mechanosensory stimulus is altered (CR). The current study investigated the potential influence of other neurotransmitter systems on this learned response. To simultaneously activate other transmitter systems at the time of learning, transgenic worm strains that express channelrhodopsin (ChR2) in either GABAergic (punc-47::ChR2) or cholinergic (punc-17::ChR2) neurons were employed. In addition, a third non-neuronal ChR2 strain was included (pmyo-3::ChR2, expressing ChR2 in body-wall muscle). Training consisted of five vibration-light stimulus pairings and acquisition was tested with a single vibration stimulus delivered either 1, 5 or 10 minutes after training. At testing, wild-type trained animals showed different locomotor responses to the vibration stimulus alone compared to controls. Upon closer examination of locomotor response components, results show that wild-type animals pause more frequently and for longer duration after conditioning. Interestingly, when cholinergic signaling was simultaneously increased during conditioning, punc-17::ChR2 animals show decreased forward response frequency and duration at test with an increased duration of backward response. With simultaneous GABAergic signaling at the time of learning, punc-47::ChR2 animals show an increase in backward response frequency and distance at test. These data suggest that both GABA and acetylcholine release can modulate conditioning of a glutamate-driven behavioral response likely by selectively altering activity in locomotor subcircuits in C. elegans.

Puhger KR, Wilmot JH, Wiltgen BW (*UC Davis*) Post-shock hippocampal activity supports trace fear conditioning - a potential role for replay ABSTRACT: Trace conditioning is a variant of classical conditioning in which termination of the CS is followed by a short interval before the US is presented. The acquisition and expression of trace conditioning has been shown to depend on the hippocampus in rats, mice, rabbits and humans. While little is known

about how the hippocampus associates these events, one proposed idea is that persistent sequential activity of single neurons in CA1 links events on the order of several seconds. However, a recent study using 2-photon calcium imaging of CA1 during trace conditioning found that the CS was not reliably encoded by the persistent activity of individual neurons, but was instead represented by CA1 population activity on longer timescales. Electrical recordings during trace fear conditioning have shown that the footshock US elicits reactivation of CA1 ensemble activity observed during the tone CS, and found that ensemble reactivation increased across training. Surprisingly, however, the learning-related increases in ensemble reactivation were more abundant after presentation of the US than during the trace interval. This finding may be related to a phenomenon called reverse replay; when an animal finds food at the end of a maze, CA1 neurons replay the path that was taken to get there in reverse order. This phenomenon is thought to play a role in associating previously experienced places with value. Our prior work has shown that optogenetic inactivation of CA1 pyramidal cells during the tone and trace interval impairs learning. Here, we use fiber photometry and optogenetics to measure and manipulate the activity of CA1 pyramidal cells during learning. Consistent with previous data, we find that the US causes a large increase in CA1 GCaMP fluorescence that is maintained for several seconds after the US. Moreover, inhibition of CA1 during this post-US period impairs memory for both the tone and context. Taken together, these data suggest that activity of CA1 pyramidal cells after the US is critical for learning. Future work will utilize electrophysiological recordings in rats to determine if hippocampal replay during the post-US period contributes to learning. SUPPORT: NIH T32 MH112507-02 to KRP; NIH T32 MH112507-01 to JHW; NIH R01 NS088053 to BJW

Rajbhandari AK, Octeau C, Chavez J, Nguyen L, Keces N, Waschek JA, Khakh B, Fanselow MS (*Icahn School of Medicine at Mount Sinai*) Optogenetic stimulation of PACAPergic pathway from basomedial amygdala to mICCs increases contextual fear behaviors ABSTRACT: While fear responses are critical for survival, exposure to extremely traumatic stimuli can cause fear regulation via certain brain regions to go awry leading some individuals to develop anxiety-related disorders like post-traumatic stress disorder (PTSD). Various brain regions, particularly the amygdala, govern fear. The amygdala microcircuitry containing the intercalated cells (ICCs) that lie in the interface of basolateral (BLA) and central amygdala are important modulators of fear behavior. We found that PACAP neurons in the basomedial amygdala (BMA) innervate the medial ICCs (mICCs). PACAP and PAC1 receptors are linked to PTSD symptom severity at both genetic and epigenetic levels, and this link was stronger in females with PTSD. We investigated whether optogenetic stimulation of BMA would alter aspects of fear behaviors including acquisition, generalization, retention or extinction via the mICCs. Our results show that BMA PACAP stimulation enhances fear retention and decreases extinction. Ex vivo optogenetic stimulation of this pathway increases excitatory postsynaptic currents (EPSCs) in mICCs neurons. Application of PAC1 receptor antagonist, PACAP 6-38 further enhanced EPSCs of mICCs neurons. Overall, these results, indicate that PACAP/PAC1 system is poised to modulate fear in a dynamic manner via the basomedial amygdala microcircuitry containing the mICCs. SUPPORT: NRSA-F32 MH10721201A1-AKR, NARSAD 26612-AKR, Staglin Center for Brain and Behavioral Health, R21MH098506 (MSF/JW MPI), RO1MH062122 (MSF)

Ramsaran AI, Kaushik R, Yeung BA, Gallucci JM, Dityatev A, Josselyn SA, Frankland PW (*The Hospital for Sick Children, Toronto, ON; University of Toronto, Toronto, ON; Canadian Institute for Advanced Research, Toronto, ON; German Center for Neurodegenerative Diseases, Madgeburg, Germany*) Maturation of hippocampal perineuronal nets underlies the ontogeny of memory specificity ABSTRACT: Compared to memories in adults, memories in infants and young children are more prone to forgetting over time (i.e., infantile amnesia; IA) and expressed less specifically (i.e., infantile generalization; IG). While biological mechanisms have been identified for IA, the neurobiology of IG remains unknown. We hypothesized that the maturation of perineuronal nets (PNNs), late-developing extracellular matrix structures known to inhibit juvenile plasticity in sensory systems, may regulate memory specificity across development. We demonstrate here that adult-like precision of hippocampus-dependent memories emerges during the fourth postnatal week (i.e., between P20 and P24) in parallel with the peak expression of PNN proteins and rapid accumulation of WFA+ PNNs around parvalbumin-expressing (PV+) interneurons in the CA1 subfield of the hippocampus. To confirm that this relationship is causal, we developed novel viral tools targeting hyaluronan and proteoglycan link protein 1 (HAPLN1) to interfere with or accelerate PNN maturation in adult and infant mice, respectively. Overexpression of a dominant-negative HAPLN1 in CA1 destabilized PNNs and re-instated infant-like generalization in adult mice. Conversely, overexpression of wild-type HAPLN1 in CA1 accelerated PNN growth and induced adult-like memory specificity in infant mice. Similar results were obtained using pharmacological manipulations of PNNs in CA1. Moreover, we establish that early-life experiences shape the trajectory of PNN maturation in the hippocampus and subsequently, the development of memory specificity. We find that adverse experiences in a model of early-life stress delay PNN and memory development such that the neural and behavioral phenotypes observed in juvenile mice resemble those of infants. In contrast, rearing pups in enriched environments during the first weeks of life led to precocial PNN growth in CA1 and memory specificity. Lastly, to address the neural circuit mechanism by which PNNs promote memory specificity, we used chemogenetics to directly manipulate the activity of PV+ cells in CA1, thus mimicking the effects of PNN manipulations on PV+ interneuron physiology. Our preliminary data show that inhibition of PV+ neurons in CA1 of adult mice during learning is sufficient re-instate infant like generalization without affecting the density of PNNs. Ongoing experiments are examining whether increasing PV+ interneuron activity promotes memory specificity in adult and infant mice lacking PNNs. Together, our findings support a role for PNNs in the development of the hippocampal memory system. We demonstrate for the first time that the maturation of PNNs in the hippocampus, which is influenced by early-life experiences and regulates inhibition in CA1 circuits, underlies the switch from memory generalization to memory specificity during childhood. SUPPORT: CIHR, NSERC, NIMH

Ray MH, Russ AN, Walker RA, McDannald MA (*Boston College*) A role for the nucleus accumbens core in adaptive fear scaling ABSTRACT: Environmental threats exist on a continuum from unlikely to certain. Adaptive behavior requires fear to scale to the level of threat. In two experiments, we determined the role of the nucleus accumbens core (NAcc) in adaptive fear scaling. In experiment 1, male Long Evans rats received bilateral neurotoxic NAcc lesions, permanently ablating NAcc neurons, or sham surgery, leaving NAcc neurons intact. In experiment 2, male Long Evans rats received bilateral NAcc viral infusions of either halorhodopsin (Halo; AAV-hSyn-eNpHR3.0-EYFP) or a control fluorophore (YFP; AAV-hSyn-EYFP) and optical ferrules dorsal to the NAcc. Following recovery, rats were trained to nose poke for food pellets then underwent Pavlovian fear discrimination in which three auditory cues were associated with unique foot shock probabilities: danger (p = 1.00), uncertainty (p = 0.25), and safety (p = 0.00). Fear was measured using suppression of rewarded nose poking. In experiment 1, rats underwent sixteen sessions of Pavlovian fear discrimination. Sham rats acquired excellent fear discrimination, showing high fear to danger, intermediate fear to uncertainty, and low fear to safety. NAcc lesioned rats failed to show the same degree of discrimination, exhibiting decreased fear to danger and increased fear to safety. This pattern was most evident when assessing fear in the first 2-s of cue onset. While shams showed evidence of discrimination in 600-ms, such discrimination was not observed in NAcc rats until nearly 2-s. In experiment 2, YFP and Halo rats underwent 10 sessions of Pavlovian fear discrimination, two sessions of cable habituation, and eight sessions of laser illumination. The final eight sessions consisted of alternating two session blocks of cue illumination or ITI illumination (12.5mW âĂŞ 532 nm light). During habituation and ITI illumination, YFP and Halo rats showed rapid, adaptive discrimination to the three cues. During cue illumination, only YFP rats achieved adaptive fear scaling. NAcc inhibition during cue presentation resulted in increased fear to safety and an inability to discriminate between safety and uncertainty only in Halo rats. Congruent with experiment 1, this pattern was specific to the first 2-s of cue onset. The results demonstrate an integral role for the NAcc in acquisition and expression adaptive fear scaling. SUPPORT: DA034010

Rose JK (*Behavioral Neuroscience Program, Department of Psychology, Western Washington University*) Classical conditioning of the C. elegans mechanosensory withdrawal response. ABSTRACT: Classical Conditioning leads to a change in behavioral response as a result of paired stimulus presentations. To take advantage of the many strengths of the C. elegans model system (mapped connectome, accessible genetic tools, etc.) to investigate neuronal mechanisms of this learning, a novel classical conditioning protocol was employed whereby a discrete mechanosensory stimulus (vibration) was paired with the onset of a light stimulus (similar to tone-shock pairing in mammals). These two sensory circuits (mechanosensation and lightsensation) allow for controlled stimulus pairing due to the ability to manipulate stimulus features (intensity, duration, etc.) and timing (onset and offset) of stimulus presentation. As well, due to the mapped connectome of C. elegans, it is known that signaling from these distinct sensory circuits converge at common postsynaptic targets; the command interneurons to drive a locomotor response. In C. elegans, generalized activation of the mechanosensory circuit (by tap or vibration) most often produces a reversal locomotor response (withdrawal response) while generalized photoactivation of the lightsensory circuit (by 350-480 nm wavelength light) typically results in forward locomotor acceleration. Originally, it was hypothesized that vibration-light pairing would result in a form of alpha conditioning by producing an increase in the worm's typical mechanosensory withdrawal response. In fact, more frequently the opposite was seen in that the post-conditioning mechanosensory response was modified and instead resembled more the lightsensation response (beta conditioning). Driving additional GABA (punc-47::ChR2) or acetylcholine (punc-17::ChR2) release during conditioning differentially affected the conditioned response. Together, findings indicate coactivation of partially overlapping neural circuits alters the response properties of those circuits and locomotor subcircuits can be differentially modulated.

Russo AS, Parsons RG (*Stony Brook University*) The Effect of Inhibition of the Infralimbic Cortex on Extinction Learning and Recall Using a Fear-Potentiated Startle Paradigm ABSTRACT: Inability to extinguish a conditioned fear response is thought to underlie the development of posttraumatic stress disorder (PTSD), and animal studies using fear conditioning have been crucial to identifying the neural mechanisms involved in aberrant fear expression and extinction. Such studies have shown that the infralimbic cortex (IL) is activated during extinction learning and recall, and that IL activation during extinction learning is necessary for subsequent extinction recall. However, most of these studies have used males as subjects, which is problematic because women are almost twice as likely as men to develop PTSD and other fear-based disorders. Moreover, nearly all of these studies have used freezing behavior as an index of fear, which might not be ideal when considering evidence that female rodents are prone to fear responses incompatible with freezing behavior. In order to determine if activation of the infralimbic cortex is necessary for extinction learning and extinction recall in female rats, we exposed adult, female, Sprague-Dawley rats to a fear-potentiated startle (FPS) paradigm: training (10 x light and foot-shock), fear recall (5 x light and startle), extinction training (30 x light alone), and extinction recall (10 x light and startle), and measured potentiation of the startle response in the presence of the light during both fear recall and extinction recall. In Experiment 1, either the GABAA agonist muscimol or saline was delivered into the IL 30 minutes prior to extinction training. We found no significant difference between rats in the muscimol and saline groups in their FPS values during extinction recall, suggesting that in females, extinction learning does not require the IL. In Experiment 2, muscimol or saline was administered to the IL 30 minutes prior to extinction recall. Preliminary results indicate that there is a trend toward rats which received muscimol prior to extinction recall exhibiting higher FPS during the extinction recall test compared to rats which received saline. Collectively, these results suggest that the IL might make unique contributions to extinction learning and extinction recall in females when measuring FPS. We are currently performing identical experiments to determine if a similar pattern is observed in male subjects.

Sangha S (*Department of Psychological Sciences and Pur-*

due Institute for Integrative Neuroscience, Purdue University, West Lafayette, IN USA) Adaptive regulation of fear and reward behaviors while learning about safety cues ABSTRACT: Guiding behavior in response to environmental cues predicting danger, safety or reward availability is necessary to survive and thrive in one's environment, and can be compromised in anxiety and addiction related disorders. Our lab is interested in how safety, fear and reward circuits integrate their functions to influence behavior, in order to better understand and treat disorders resulting from maladaptive emotion regulation. To do this, we have developed a behavioral paradigm that directly assesses the precision of fear and reward seeking behaviors in response to learned fear, safety and reward cues. With this paradigm, we have previously tested the role of the prefrontal cortex and amygdala in learning to discriminate among these cues. We have shown the infralimbic cortex (IL) is necessary for suppression of fear in response to safety cues, and that the amygdala contains neurons that respond selectively to safety cues. Our current unpublished work demonstrates increased neural activity in the IL during the co-presentation of fear and safety cues, indicating the IL is engaged during active fear suppression. We also observe strong sex differences in learning to discriminate among the fear, safety and reward cues, with females displaying elevated reward seeking to the reward cue, and increased fear behavior during the safety cue. We are now beginning to identify what the possible neuronal correlates could be to explain how these behavioral sex differences in response to these conflicting cues are being manifested. SUPPORT: R01 MH110425

Sarikaya K, Pil B, Marriott J, Taber K, Vinton E, Crocker A (*Middlebury College*) A novel mediator of pain memory in adult Drosophila melanogaster. ABSTRACT: The detection, learning, and recall of painful events is crucial to all animals' survival. Here we asked what happens in an individual's brain (in this case, the fruit fly) when they are exposed to a physically painful stimuli. The most striking gene expression changes occur following the painful event itself. One of the genes changing is NinaA, which appears to play a part in painful memory formation and stress behavior in the fly. Previously, NinaA has only been characterized within the context of its interactions with Rhodopsin 1 in the eye. We find flies carrying a mutation in the NinaA gene fail to form long-term, aversive odor memories as well as fail to avoid electric shock during training. Interestingly they do appear to show normal short-term learning. Our data suggests that NinaA animals generate a stress response to noxious stimuli, as measured by an increase in wall following behavior, but once that noxious stimuli is removed the heightened stress response ends. This is in contrast to wild type flies who show enhanced stress responses following painful stimuli exposure. We hypothesize that this failure to maintain a normal stress response to painful stimuli reduces their capacity to maintain long-term memories. We also hypothesize that this is mediated through the DAL neuron. Further characterization of both the NinaA gene and the DAL neuron will shed light on the role ancient stress pathways play in memory formation in the fly. SUPPORT: Vermont Genetics Network and NIGMS

Scaplen KM, Talay M, Salamon S, Nunez K, Waterman G, Gang S, Song SL, Barnea G, Kaun KR (*Brown University*) Circuits that encode and express alcohol -associated preference ABSTRACT: Substance use disorders are chronic relapsing disorders often impelled by enduring memories and persistent cravings. Alcohol, as well as other addictive substances, remolds neural circuits important for memory to establish obstinate preference despite aversive consequences. How pertinent circuits are selected and shaped to result in these unchanging, inflexible memories is unclear. Using neurogenetic tools available in Drosophila melanogaster we define how circuits required for alcohol associated preference shift from population level dopaminergic activation to select dopamine neurons that predict behavioral choice. During memory expression, these dopamine neurons directly, and indirectly via the mushroom body (MB), modulate the activity of interconnected glutamatergic and cholinergic output neurons. Transsynaptic tracing of these output neurons revealed at least two regions of convergence: 1) a center of memory consolidation within the MB implicated in arousal, and 2) a structure outside the MB implicated in integration of naÃŕve and learned responses. These findings provide a circuit framework through which dopamine neuron activation shifts from reward delivery to cue onset, and provides insight into the inflexible, maladaptive nature of alcohol associated memories.

Schmid S, Scott K, Moehrle D (*Anatomy & Cell Biology, Schulich School of Medicine & Dentistry, University of Western Ontario*) Cognitive testing in an animal model for autism ABSTRACT: Autism spectrum disorders (ASD) are complex neurodevelopmental disorders that are caused by genetic and/or environmental impacts, often probably by the interaction of both. They are characterized by deficits in social communication and interaction and by restricted and repetitive behaviours and interests from early childhood on, causing significant impairment. The latest DSM-5 also acknowledges for the first time sensory processing disruptions as core symptoms of autism. While it is clear that no animal model captures the full complexity of ASD in humans, genetic models are extremely useful for studying specific symptoms associated with ASD and the underlying cellular and molecular mechanisms, as well as testing therapeutic approaches. We use different highly translatable implicit and perceptual behavioural tasks to probe for changes in auditory processing a different stages along the sensory pathways in a genetic rat model. Our results reveal a stunning resemblance of auditory processing disruptions in the rat model and autistic individuals across postnatal development. SUPPORT: BrainsCAN (Canada First Research Excellence Funds), Simons Foundation for Autism Research (SFARI)

Schoenbaum G (*NIDA-IRP*) Dopaminergic prediction errors are necessary for updating orbitofrontal representations of expected outcome value and identity ABSTRACT: Transient changes in the firing of midbrain dopamine neurons are proposed to act as prediction errors to support some forms of learning in the brain. We have recently shown that these phasic changes track errors in predicting both a reward's value as well as its sensory features. This basic finding has been corroborated in humans by work from Kahnt and colleagues showing that bold response in human midbrain also reflects both types of errors; Kahnt et al further showed that the strength of these errors was correlated with updates in associative information reflected in bold response in the orbitofrontal cortex,

suggesting that dopaminergic errors were driving learning in this downstream region. Here we provide a causal test of this hypothesis. We infused a virus containing a cre-dependent form of NpHR2 into the ventral tegmental area of TH-Cre rats, implanted recording electrodes in the lateral OFC where dopamine inputs are concentrated, and then recorded in an odor guided choice task in which the value and identity of the expected rewards were manipulated across blocks of trials. In some blocks, orange/yellow light was delivered into midbrain in the first 20 trials of the block precisely when the new reward was delivered, in order to prevent phasic firing of dopamine neurons; in other blocks,blue light was delivered as a control. Preliminary analyses of the behavior and neural activity showed that when orange/yellow light was delivered to shunt dopamine transients, the rats were slower to switch their behavior to reflect new values, and orbitofrontal neuron ensembles were poorer at encoding the new value and identity expectations, relative to blocks in the same sessions when blue light was delivered. These results provide causal evidence that dopamine transients proposed to serve as teaching signals are necessary to support updating of associative representations relevant to predicting both the value and the identity of expected reward in the orbitofrontal cortex. SUPPORT: NIDA-IRP

Seamans J (*UBC*) Conditioning to emotional events by Anterior Cingulate Cortex neurons ABSTRACT: The Anterior Cingulate Cortex (ACC) responds to outcomes of a positive or negative valence, but past studies typically focus on one valence or the other, making it difficult to know how opposing valences are disambiguated. We recorded from ACC neurons while pairing different tone CSs with aversive, appetitive or null outcomes. The responses to the different tones/outcomes were highly inter-mixed at the single neuron level but combined to produce robust valence-specific representations at the ensemble level. The valence-specific patterns far outlasted the tones and outcomes, persisting throughout the long inter-trial intervals (ITIs) and even throughout trial blocks. When the trials were interleaved, the valence-specific patterns abruptly shifted at the start of each new trial. Overall the aversive trials had the greatest impact on the neurons. Thus within the ACC, valence-specific conditioning is largely an emergent property of ensembles and valence-specific representations can appear quickly and persist long after the initiating event.

Seemiller LR, Gould TJ (*Department of Biobehavioral Health, Penn State University, University Park, PA*) Ethanol differentially induces fear learning deficits in adolescent and adult male and female C57BL/6J and DBA/2J inbred mice. ABSTRACT: Age and genetic background can influence susceptibility to the negative consequences of alcohol abuse. Adolescents are often less sensitive than adults to acute negative consequences of alcohol. This may make them more likely to start abusing alcohol during adolescence and develop adult addictive disorders. In this study, adolescent and adult mice of two inbred strains, C57BL/6J and DBA/2J, were treated with ethanol prior to fear conditioning training. One day and 7-8 days later, they underwent contextual and cued testing. C57BL/6J mice showed greater contextual learning deficits than DBA/2J mice, suggesting that C57BL/6J mice are more susceptible to ethanol-induced contextual learning deficits. These deficits persisted one week after training. Male DBA/2J mice showed greater contextual learning deficits than female DBA/2J mice, suggesting this learning deficit is sex-dependent in the DBA/2J strain. This male-specific contextual learning deficit in the DBA/2J strain warrants further study. Additionally, our study adds to the growing body of literature showing that C57BL/6J and DBA/2J mice have different responses to alcohol. Future studies can investigate the genetic substrates that mediate this strain difference. SUPPORT: Jean Phillips Shibley Endowment

Sharpe M (*University of California, Los Angeles*) Reward learning shapes the fear circuit ABSTRACT: The Lateral Hypothalamus (LH) has been traditionally viewed as providing an innate drive to approach rewards as dictated by other "cognitive" structures, such as prefrontal cortex. However, we have now shown that the GABAergic population in LH encodes learnt associations between cues and rewards (Sharpe et al., 2017, Current Biology). This allows LH to contribute to more complex forms of behaviour without input from higher-order structures. Given this new research, we were interested to see whether the role for the LH in cognition would be seen when learning to encode fear memories. Accordingly, we optogenetically inactivated LH GABAergic neurons during fear learning. Interestingly, we found that these neurons were not involved in learning to associate cues with mild foot shocks in naive rats. However, if these rats had previously learnt to associate cues and rewards, GABAergic neurons then became necessary for rats to learn about the predictors of fear. Control experiments showed that this dissociation could not be accounted for by generalisation between fear and reward learning in these procedures. Effectively, having prior experience with learning about rewards shaped the neural circuits that were involved in learning about fear. These data have important consequences for the treatment of trauma-related disorders as they suggest previous experience could change where the fear memory is encoded.

Shrestha P[1,‡], Shan Z[1], Marmarcz M[1], Zerihoun AT[1], Chien-Yu J[1], San Agustin Ruiz K[1], Herrero-Vidal PM[1], Pelletier J[2], Heintz N[3], Klann E[1,4,‡] ([1]*Center for Neural Science, New York University, New York, NY 10003;* [2]*Department of Biochemistry, McGill University, Montreal, Quebec;* [3]*Laboratory of Molecular Biology, The Rockefeller University, New York, NY 10065;* [4]*NYU Neuroscience Institute, New York University School of Medicine, New York, NY*) De novo translation in distinct centrolateral amygdala interneurons is required for long-term emotional memories ABSTRACT: To survive in a dynamic environment, animals need to identify and appropriately respond to stimuli that signal danger. Species-specific defensive behaviors and autonomic responses are elicited upon encountering a stimulus predictive of threat. On the other hand, survival of foraging animals also depends on threat response inhibition during a stimulus that predicts absence of threat, i.e. safety. A hallmark feature of post-traumatic stress disorder (PTSD) is the inability to suppress defensive behavior even under safe conditions. Understanding the biological substrates of differential threat memories in which animals learn to flexibly switch between expressing and suppressing defensive responses to a threat-predictive cue and a safety cue, respectively, is critical for developing treatments for memory disorders such as PTSD. A key brain

region for processing, storing, and retrieving threat memories is the centrolateral amygdala (CeL) that has been described exquisitely at the level of precisely interconnected neural subpopulations using opto- and chemogenetic techniques to control neuronal activity. However, little is known about regulation of the downstream protein synthesis machinery in specific neuronal cell types in the CeL, an important area of study considering consolidation of long-term, but not short-term, threat memories requires de novo translation. Herein, we describe the development of intersectional chemogenetic strategies to block translation initiation sensitive to levels of eukaryotic initiation factor 4E (eIF4E) and phosphorylated eukaryotic initiation factor 2Îś (p-eIF2Îś) in a temporally controlled, cell type-specific manner. Using these cell type-specific protein synthesis inhibition (ciPSI) strategies, we show that discrete CeL interneurons expressing Somatostatin (SOM) and Protein Kinase CÎt' (PKCÎt') make distinct, yet complementary contributions to consolidation of a differential threat memory. We find that time-limited disruption of protein synthesis in SOM interneurons impairs long-term freezing response to the threat-predictive cue, whereas protein synthesis in PKCÎt' interneurons is required for long-term suppression of defensive response to the safety cue. Further, we show that oxytocinergic neuromodulation of PKCÎt' interneurons during differential threat learning plays a key role in long-lasting discrimination of cues with opposite valence. Our results show that elements of a differential threat memory are compartmentalized in distinct CeL interneuron populations and provide new mechanistic insight into the role of protein synthesis in consolidation of long-term memories.

Sillivan S (*Temple University; The Scripps Research Institute-Florida*) microRNA regulation of persistent stress-enhanced memory ABSTRACT: Mechanisms supporting long-lasting, remote memory are largely unknown, yet highly relevant to neuropsychiatric disorders of memory, such as posttraumatic stress disorder (PTSD). PTSD is a chronic, debilitating disorder in which patients exhibit memories of trauma that are heightened, perseverant and extinction-resistant. Nearly everyone experiences at least one traumatic event in their lifetime, but only 10-20% will later display enduring symptoms of PTSD. We developed a stress-enhanced fear learning (SEFL) paradigm in inbred C57BL/6 mice that results in PTSD-like characteristics, including persistently enhanced memory in a subset of mice termed stress stress-susceptible (SS). Importantly, this SEFL protocol allows for the study of molecular phenotypes associated with selective vulnerability, as SS mice can be identified from training data, avoiding mechanistic confounds introduced by additional phenotyping. Relative to stress-resilient animals (SR), SS mice have heightened cFos activation in the basolateral amygdala complex (BLC) upon retrieval of the remote stress memory (30 days post-training) and differential BLC expression of genes with known polymorphisms in human PTSD genomic studies. Disruption of persistent, stress-associated memories is relevant for treating PTSD and microRNAs (miRNAs) are excellent remote memory candidate regulators. miRNAs are endogenous 20-24 nucleotide RNAs that act as translational repressors through direct binding to the 3'-UTR of target mRNAs and noncleavage degradation of the target mRNA via deadenylation. miRNAs have a wide genomic range of potential target proteins that confers a complexity capable of handling the intricacies of memory but, the contribution of miRNAs to long-lasting, stress-enhanced remote (>30 days) memory is unknown. We performed small-RNA sequencing and quantitative proteomics on BLC tissue from SEFL animals collected one month after training and identified persistently changed miRNAs associated with PTSD-like heightened fear expression. Functional manipulations of two candidate miRNAs, mir-135b-5p and mir-598-3p, modulated stress-associated memory in SEFL animals without impacting baseline anxiety levels. Importantly, both miRNAs are conserved from mouse to human. We detected mir-135b-5p expression in human amygdala and its passenger strand was elevated in serum from a well-characterized Dutch PTSD military cohort. Thus, miRNAs may represent important therapeutic targets for dampening persistent, stress-enhanced memory. SUPPORT: DA041469

Smith NJ, Trott JM, Fanselow MS (*UCLA*) Fear, avoidance and punishment: Impact of shock intensity on voluntary vs involuntary processes. ABSTRACT: To the learning theorist, an avoidance response is a behavior that precludes an aversive event and is acquired and maintained by a reinforcement contingency such as the response-contingent termination of a warning signal or elimination of an impending aversive outcome. Some accounts of avoidance performance postulate that the presence of such instrumental contingencies provides alternative strategies that replace innately programmed fear responses. On the other hand, biologically oriented views of fear argue that high levels of fear limit behavioral repertoires to species-specific defense reactions (SSDRs) that cannot be controlled by instrumental contingencies. We thus examined whether male and female Long-Evans rats could learn avoidance, or punishment contingencies under high vs low levels of fear. We targeted the dominant SSDR, freezing, during an auditory warning signal, as the criterion response using different shock intensities (0.8 vs 0.25 mA). We hypothesized that at the lower shock intensity, behavioral flexibility will be such that the animal will show some contingency learning. At both shock intensities, the most striking difference between conditions was that rats in the punished groups received far more shocks than the avoidance groups. This was because across both shock intensities, these schedules produced high levels of freezing (30-80%) that showed little difference between groups. In other words, the available operant contingencies (CS termination and shock avoidance) provided no evidence for instrumental control of behavior. While we did not see explicit evidence of instrumental learning at either shock intensity, we saw evidence of different time-courses of fear levels across trials each day, depending on shock intensity. Overall, total shocks received across shock intensities were similar, but at 0.8 mA punished animals received more shocks in the first five trials of each day, whereas at 0.25 mA punished animals received fewer shocks in the first five trials. The opposite pattern was observed in the avoidance animals. These patterns may be explained by the animals at 0.8 mA beginning each session at a higher position on the predatory imminence continuum. Predatory Imminence Theory organizes defensive behavior according to perceived proximity to a threat, such that as threat levels increase, animals progress through states of anxiety, then fear and then panic. At 0.8 mA, perhaps animals began in a fear state and progressed into a panic state, reducing freezing as the session progressed. At 0.25 mA, perhaps animals began in an anxiety state and progressed into a fear state, increasing freezing

as the session progressed. The observed fear-related behavior was fully predicted by the most basic of Pavlovian principles, CS-US association. Because fear produced by the tone elicited freezing, punishment animals received a higher probability of CS-US pairing than avoidance animals. The failure for punishment to suppress freezing is difficult for reinforcement theories to explain as those animals could both avoid the shock and terminate the CS by doing anything other than freezing, yet freezing dominated behavior. These findings have major implications for the use and interpretation of avoidance learning as a method for studying fear.

Souza RR, Rennaker RL, Hays SA, Kilgard MP, McIntyre CK (*The University of Texas at Dallas, Richardson-TX.*) Tackling fear memories using vagus nerve stimulation ABSTRACT: Exposure-based therapies are the "gold-standard" psychotherapies used to treat the maladaptive fear and other symptoms in Posttraumatic Stress Disorder (PTSD). These therapies are designed to extinguish conditioned fear through repeated exposure to reminders of traumatic experiences in the absence of the negative consequence. Unfortunately, large clinical trials have yielded nonresponse rates that can exceed 50% on some measures. Vagus nerve stimulation (VNS) has emerged as a promising strategy to enhance extinction learning by promoting therapeutic synaptic plasticity in the fear network. Here we present our recent findings in rodents demonstrating that VNS enhances extinction learning and reduces fear return in different models of PTSD using mild and severe stress. We also show that VNS can attenuate the non-associative symptoms of PTSD, including increased anxiety, reduced sociability and hyperarousal. VNS promotes generalization of extinction to associated fear cues that were not presented during therapy. The efficacy of VNS follows an inverted-U function for stimulation intensity. Short VNS bursts can be as effective as long VNS trains while delivering much less stimulation. The enhancing effects of VNS are found when stimulation is delivered during cue presentation, but not when delivered only between cue presentations. The high temporal precision of the therapy is consistent with earlier studies demonstrating that phasic bursts of the neuromodulators acetylcholine, norepinephrine and serotonin are responsible for the therapeutic effects of VNS during extinction. We will conclude by summarizing our plans to test VNS during prolonged exposure therapy in people with PTSD.

Spencer GE, Carpenter S, Rothwell CM, de Hoog E, Walker S (*Dept. of Biological Sciences, Brock University, ON. Canada.*) Enhancing and extending memory: why vitamins might like the dark. ABSTRACT: The Vitamin A metabolite, retinoic acid, is important for memory formation and acts by binding to nuclear retinoid receptors to influence gene transcription. In vertebrates, disrupting retinoid signaling in the brain can impair novel object recognition, spatial working memory and hippocampal plasticity. We now show that retinoid signaling can also play a role in memory formation in some invertebrates. I will describe how retinoids enhance and extend memory following conditioning of the mollusc Lymnaea stagnalis. Interestingly, exposure to constant darkness was found to induce similar effects. When probing the mechanisms involved, we discovered signaling interactions between darkness and retinoids, with darkness affecting retinoid receptor expression, as well as inducing changes in a key neuron mediating the conditioned behaviour. SUPPORT: Natural Sciences and Engineering Research Council (NSERC) of Canada.

Teratani-Ota Y, Lafreniere M, Wiltgen BJ (*UC Davis*) Segregated object and context processing in CA1 ABSTRACT: The hippocampus is thought to combine "what" and "where" information from the cortex so that objects and events can be represented within the spatial context in which they occur. Surprisingly then, these distinct types of information remain partially segregated in the output region of the hippocampus, area CA1. The proximal segment of CA1 receives direct input from the medial entorhinal cortex (which encodes spatial context) whereas distal CA1 receives a direct projection from the lateral entorhinal cortex (which encodes objects and odors). This distinct organization suggests that the function of CA1 may differ along its proximo-distal axis. To test this idea, we quantified c-fos expression in proximal and distal CA1 after exposing mice to a novel context or novel objects. Consistent with previous reports, we found that exposure to a novel context increased c-fos expression in proximal CA1 while exposure to novel objects increased c-fos activity in distal CA1 (compared to appropriate control groups). Using halorhodopsin (NpHR), we are in the process of silencing these distinct segments during memory retrieval of object and context representations. To examine the role of proximo-distal CA1 in object-related memories, we will use the novel object location task. In this task, mice are exposed to a pair of identical objects in a habituated environment and later tested for memory by moving one of the objects to a new location. As mice are innately motivated to explore novelty, they should spend more time exploring the object that moved than the stationary object. We predict that silencing distal CA1 during testing will impair mice's ability to discriminate between novel and familiar objects. We will also use a contextual fear conditioning task that utilizes a context pre-exposure and immediate shock training to examine the rapid retrieval of contextual representations. This task has been shown to require integration of a previously formed context representation and a foot shock. Thus, we predict that silencing proximal CA1 during the training session will prevent retrieval of the context representation required to form a fear memory, which will result in an impaired freezing behavior at testing. Our work will lead to a better understanding of how different information is stored in the hippocampus.

Totty MT, Warren N, Ramanathan K, Ressler R, Maren S (*Department of Psychological and Brain Sciences and Institute for Neuroscience, Texas A&M University, College Station, TX 77843-3474*) Neural circuits mediating context-dependent flight behavior in rats ABSTRACT: Fadok and colleagues (2017) have developed a modified Pavlovian fear conditioning procedure in which a serial conditioned stimulus (SCS) consisting of serial presentations of pure tone (7 kHz) and white noise (1-20 kHz), followed by a footshock unconditioned stimulus (US). After conditioning, mice exhibit freezing to the tone, but transition to flight (e.g. escape jumps and increased movement speed) during the noise. The transition from freezing to flight behavior is gated by the central nucleus of the amygdala (CeA), and flight responses are only elicited within the conditioning context (Fadok et al., 2017). Here, we replicate these behavioral findings in male and female Long-Evans rats and further

investigate how flight responses are contextually regulated. After SCS conditioning, rats either received unsignaled footshocks in a novel context (Shock) or were exposed to the same novel context for an equal amount of time (No-Shock). The next day, Shock animals displayed flight responses to SCS-alone presentations within the unsignaled footshock context, whereas No-Shock animals did not. Moreover, extinguishing contextual fear following conditioning suppressed the expression of flight responses. We therefore conclude that flight responses are dependent upon contextual fear, irrespective of where SCS conditioning occurs. The bed nucleus of the stria terminalis (BNST), central amygdala (CeA), and the ventral hippocampus (VH) have been implicated in contextual fear. Reversible inactivation of either the CeA or the VH diminishes flight responses in the conditioning context, whereas inactivation of the BNST successfully reduced context fear without blocking flight responses. These findings advance our understanding of the neural circuitry underlying the contextual regulation of active defensive behavior by demonstrating that flight responses are dependent upon contextual fear and that this effect appears to be mediated by the CeA and VH.

Trask S, Pullins SE, Helmstetter FJ (*University of Wisconsin-Milwaukee*) Distinct Roles of the Anterior and Posterior Retrosplenial Cortices in Encoding, but not Retrieval, of Trace Fear Memory ABSTRACT: The retrosplenial cortex (RSC) has a prominent role in memory and has dense reciprocal connections with other brain regions important for memory formation and retrieval including the hippocampus and prefrontal cortex. Trace fear conditioning, in which a neutral conditional stimulus (CS) is followed by a brief stimulus-free interval before a footshock (the unconditional stimulus or UCS), is a powerful method used to study memory in rats and can be separated into encoding (e.g., original learning) and retrieval (later performance to the CS) phases. Importantly, this type of learning incorporates information about the environment in which learning takes place ("where" information) with information about the CS ("what" information). While most research on encoding and retrieval of trace fear memory has focused on the hippocampus and prefrontal cortex, recent data has begun to suggest a critical role for the RSC in trace memory encoding. In two experiments, we tested the hypothesis that the posterior region of the retrosplenial cortex (pRSC, which is closely interconnected with the hippocampus) would have a selective role in both encoding and retrieval of context-related information while the anterior portion (aRSC) would be important for processing event-related (e.g., CS-UCS) information. Using optogenetics, either the aRSC or pRSC was silenced precisely during the CS-UCS period on training trials during memory encoding (Experiment 1) or during the CS period of retrieval testing (Experiment 2). In Experiment 1, we found that silencing the aRSC during acquisition resulted in a selective impairment in responding to the CS during retention testing, whereas silencing the pRSC during acquisition resulted in impaired responding to the training context. However, in Experiment 2 silencing of either region resulted in impaired CS freezing. Preliminary data quantifying immediate early gene (e.g., zif268) expression in RSC support effective and anatomically selective inhibition of neural activity. Together, these results suggest that while encoding of trace fear conditioning relies on distinct "where" and "what" circuits, both regions are needed later expression of that memory. While the role of the retrosplenial cortex has been demonstrated in other paradigms examining contextually-bound learning, these results suggest distinct roles for the anterior and posterior regions of the retrosplenial cortex in the encoding, but not retrieval, of trace fear memory. SUPPORT: NIH MH069558 (FJH)

Trott JM, Adison R, Fanselow MS (*UCLA*) Sex differences in contextual fear learning and generalization. ABSTRACT: Contextual fear learning can be used to study the acquisition and generalization of a fear memory. Therefore, it is a useful model to study learning processes relevant to healthy functioning and mental illness, particularly those related to anxiety disorders. Contextual fear generalization is especially relevant to anxiety disorders, which are often defined by expressing fear and/or anxiety in safe contexts. Anxiety disorders are sexually dimorphic with regard to occurrence and severity of episodes such that females tend to experience more frequent and more severe episodes. Presented here are a series of experiments examining contextual fear learning in male and female rats, with a focus on generalization. With some variation, these experiments use a 3-day procedure in which Day 1 consists of pre-exposure to the to-be-shocked context, Day 2 consists of a single context-shock pairing, and Day 3 consists of testing in either the same or a novel environment. Increasing the amount of pre-exposure on Day 1 or time before shock (placement-to-shock-interval; PSI) on Day 2 both lead to enhanced conditioning. It is unknown if these periods use the same process such that they are simply additive or if there are different processes underlying the learning during each period. Historically, male rats tend to show greater contextual fear than females at low PSI's, and this effect can be abolished by a sufficiently long pre-exposure session. Thus, for these experiments, relatively short pre-exposure and PSI's are used to determine any sex differences in fear learning. The BACON model is a conceptual and computational model of hippocampal contextual learning. One of the major suggestions of the model is that the hippocampus can have two functional modes, one for building a contextual representation (which would mostly happen during pre-exposure) and one for retrieving that representation, prior to shock for example (which would happen during Day 2's PSI). It was found that pre-exposure timing and PSI timing were not equivalent to each other. Animals with 120s of pre-exposure and a 30s PSI show a differential level and time-course of fear expression than animals who received 30s of pre-exposure and a 120s PSI, and this further depended on sex of the rat. With longer pre-exposure periods, female rats show greater contextual fear and more evidence of discrimination. With shorter pre-exposure periods, male rats show more contextual fear and evidence of discrimination, consistent with previous literature. To examine the potential associative nature of the male and female contextual fear memories, an experiment comparing recently vs remotely acquired contextual fear was run. Males were again shown to have greater contextual fear at both time points, and this contextual fear incubated over time in males, but not females

Twining RC, Kirry A, Herbst M, Martinez-Cabrera V, Gilmartin MR (*Marquette University*) Mediodorsal thalamic input to prelimbic cortex is required for trace and context fear memory formation. ABSTRACT: The prelimbic medial prefrontal cor-

tex (PL mPFC) receives afferent input from the amygdala, insula, mediodorsal thalamus (MD), and the ventral hippocampus (VH). It is an integral component of a neural system that mediates cognitive and emotional processes and regulates a wide range of adaptive behaviors (Hiser and Koenigs, 2018). In humans, dysfunction of the PFC and its functional connections is associated with anxiety disorders and post-traumatic stress disorder. In animal models, the mPFC is critically involved in cognitive and emotional aspects of conditional fear expression, extinction, and renewal, the encoding of aversive locations, prospective or temporal encoding, and spatial working memory (Ramanathan et al., 2018; Marek et al., 2018; Sharpe and Killcross, 2015, Spellman et al., 2015; Sotrez-Bayon, 2012). During the acquisition of fear conditioning, the PL is required for cued and contextual fear learning when a temporal gap, or trace interval, is imposed between the auditory conditional stimulus (CS) and shock unconditional stimulus (UCS) but not when they are temporally contiguous, as in standard delay conditioning. Indeed, PL neurons exhibit sustained increases in learning-related neuronal firing to the CS that bridges the trace interval (Gilmartin & McEchron, 2005) and optogenetic silencing of this activity blocks the formation of a trace fear memory (Gilmartin et al. 2013). While PL activity mediates cued and contextual fear during trace fear conditioning, it is unknown which afferent inputs support learning or learning-related neuronal spiking. We have shown that optogenetic silencing of VH input to PL during the acquisition of trace conditioning significantly impairs contextual fear memory but could be restored if the VH-PL was silenced once again during retrieval. Interestingly, VH input to the PL was not required for trace cued fear memory (Twining et al., in revision). Given the similar density of afferent input to PL cortex from the VH and MD, their demonstrated importance for spatial working memory, and because MD inputs to PL sustain prefrontal neuronal activation across temporal delays during spatial working memory tasks (Bolkan, 2017), we hypothesized that the MD inputs to PL may be required for trace cued fear memory and might also regulate PL activity. Here we injected rats with AAV9/CAG-ArchT-GFP into the MD (500 nl/side) and implanted optic fibers 0.5 mm above the terminals in PL or cell bodies in the MD. We silenced during a 2-trial TFC protocol and repeated for 3 days. Cued and contextual fear was tested without silencing after each 2-trial block. Results indicate that MD thalamus projections to PL are essential for both trace cued and contextual fear memory formation. Direct silencing of the MD nucleus, however, produced larger impairments to context fear that emerge earlier in training and smaller, less reliable impairments in trace cued fear memory. Moreover, while loss of VH input was largely associated with increased PL activity, loss of MD input produced heterogenous responses in PL firing. Future experiments will determine if these response types correspond to cued vs. contextual memory. Together with our previous findings, these data suggest that the prelimbic contribution to cued fear in a trace paradigm normally engages MD input but can support cued fear in the absence of MD. In contrast, contextual fear is highly sensitive to the loss of either thalamic or hippocampal input to the PL.

Vega-Villar M, Horvitz JC, Nicola SM (*Psychology Dept., Graduate Center, CUNY, New York, NY; Psychology Dept., City College of New York, CUNY, New York, NY; Dept. of Neuroscience, Albert Einstein College of Medicine, The Bronx, NY*) Experience-dependent changes in the nucleus accumbens underlie acquisition of cued reward-seeking behavior: contribution of NMDARs ABSTRACT: Animals learn associations between contextual cues and the natural rewards they predict. As a result, reward-predictive cues come to trigger approach to locations where rewards are available. The nucleus accumbens (NAc) in the ventral striatum is implicated in the expression of such cued reward-seeking behaviors. Accordingly, many neurons in the NAc become excited upon presentation of an already-learned reward-predictive cue. Cue-evoked excitations encode the motivational value of the stimulus and are required for expression of the subsequent approach. However, whether and how cue-evoked excitations emerge during learning has not yet been established. In Experiment 1, we recorded the unit firing activity of NAc core neurons as rats learned to approach a reward receptacle upon presentation of a cue. Our results indicate that cue-evoked excitations begin to increase a few trials before cued approach behavior is detected and they continue to escalate as cued reward-seeking responses become more vigorous. Because infusion of NMDA receptor antagonists into the NAc during training impairs acquisition of similar reward-oriented behaviors, we hypothesized that the emergence of cue-evoked excitations during cued approach learning is due to NMDA receptor-dependent plasticity within the NAc. In Experiment 2, we performed colocalized simultaneous unit recordings and NMDA receptor antagonist microinfusions in the NAc. We found that the potentiation of learning-related cue-evoked signals in the NAc depends on NMDA receptor-dependent plasticity within this structure. Our results link accumbens plasticity, changes in striatal activity and the emergence of conditioned behavior, revealing a neural mechanism via which the NAc participates in associative learning.

Webb EK[1,2], Cutright E[1], Schneider M[1], Mwampashi R[3], Cox C[1], Fast CD[1] ([1]*APOPO [AntiPersoonsmijnen Ontmijnende Product Ontwikkeling];* [2]*University of Wisconsin-Milwaukee, Milwaukee, Wisconsin;* [3]*Sokoine University of Agriculture, Morogoro, Tanzania*) Training African giant pouched rats as biosensors: New humanitarian applications. ABSTRACT: Since 1997, APOPO, a global non-profit organization with headquarters in Tanzania, has trained African giant pouched rats (Cricetomys ansorgei) to save lives. The rats detect buried landmines in post-conflict zones in Africa and Southeast Asia where they have safely found over 107,500 explosives to date. The rats also help combat the world's deadliest infectious disease, tuberculosis (TB), by re-screening sputum samples from presumptive patients, enabling the rats to find nearly 15,000 cases of TB that were initially missed by traditional diagnostics. APOPO's operational success is supported by multifaceted research to inform and optimize current training procedures and develop novel scent-detection applications. Recent proof-of-principle projects explored new humanitarian applications for the rats, including their potential to sniff out illegally trafficked wildlife products and the zoonotic disease, Brucellosis. Laboratory trials suggest the rats can readily learn to identify the unique odor-profiles of these targets, including when they occur in novel combinations with other substances. For wildlife detection, the rats were challenged to find pangolin (the world's most widely smuggled mammal) and hardwood (threatened by illegal logging) hidden among items commonly used to mask their smell when they are smuggled, while rats trained to find cultured brucella were tested to distinguish

between spiked and non-spiked fecal samples. Promising results from these tests lay the groundwork for developing unique deployment strategies that leverage the rats' versatility, efficiency, and mobility as cost-efficient solutions to these global challenges.

Wilmot JH, Lafreniere MM, Wiltgen BJ (*University of California, Davis*) Increased c-Fos expression in a TetTag transgenic mouse line. ABSTRACT: Memory retrieval is thought to occur when neurons that were engaged during learning are later reactivated. Until recently, testing this prediction has been difficult due to technical limitations. However, newly developed molecular and genetic techniques now allow researchers to test this idea by selectively tagging and manipulating cells that were active during learning. One popular approach to labeling these cells is to use the fos-tTA transgenic mouse (TetTag). In these mice, active (c-fos+) neurons express the tetracycline transactivator (tTA), which can be used to drive the expression of other proteins under the tetO promoter in order to identify (fluorescent proteins) and/or control (opsins, DREADDS) these cells. Importantly, tagging is restricted to periods when there is no doxycycline present in the animals' diet, allowing selective tagging of neurons activated during a specific experience. In addition to tagging cells active during learning, it is common to examine the reactivation of these cells using immediate early gene (IEG) expression as an index of neural activity. There are currently several different TetTag lines available. In our previous work, we received the original mouse line from Dr. Mark Mayford, which is also available from MMRRC. Jackson Labs provides a different version of this mouse, which expresses both fos-tTA and fos-shEGFP. In the current experiments, we examined IEG expression in this line and compared it to our previous work. Surprisingly, we found that fos-tTA/fos-shEGFP mice express increased levels of c-fos in the hippocampus compared to wild type animals under a variety of behavioral conditions. However, the expression of other IEGs, such as arc and egr-1, were not elevated in fos-tTA mice, suggesting that the overexpression of c-fos is not the result of increased excitability or broad changes in gene expression. Inspection of the fos-shEGFP plasmid sequence revealed that it contains a portion of the endogenous c-fos gene that encodes the N-terminus of the protein. This is problematic because the majority of commercially available antibodies detect some portion of this amino acid sequence. Therefore, we hypothesize that c-Fos, but not other IEGs, appears elevated in these mice because antibodies detect both the endogenous protein and the shEGFP protein. If this hypothesis is correct, single transgenic fos-tTA animals (available from MMRRC) will not present the same issue. These results illustrate a major limitation inherent in the use of fos-tTA/fos-shEGFP transgenic mice and provide potential solutions to this issue. SUPPORT: NINDS RO1 NS088053 to BJW and NIMH T32 MH112507-01 to JHW

Wright DW, Bodinayake KK, Kwapis JL (*Penn State University*) Pharmacological HDAC3 inhibition ameliorates age-related updating impairments in the novel OUL updating paradigm. ABSTRACT: Memories are not stored as permanent records of experience but instead are dynamically modified in response to new information. In fact, most memories are updates to existing information, rather than de novo associations. Despite its fundamental importance, the molecular mechanisms that underlie memory updating are unclear. Further, although memory updating is impaired with age, the mechanisms that underlie this deficit are unknown. As transcription is both important for memory updating and altered with age, dysfunctional epigenetic machinery may contribute to age-related impairments in memory updating. Altered histone acetylation in particular has been implicated in age-related memory decline; acetylation at histone 4, lysine 12 (H4K12Ac) is altered in the aging hippocampus and inhibition of the repressive histone deacetylase 3 (HDAC3) can ameliorate age-related impairments in memory formation. Here, we tested whether HDAC3 may also contribute to age-related deficits in memory updating. To this end, we combined pharmacological inhibition of HDAC3 with a novel behavioral task we developed specifically to study memory updating, called the Objects in Updated Locations (OUL) task. To determine the role of HDAC3 in memory updating, we first systemically injected mice with the pharmacological HDAC3 inhibitor RGFP966 immediately after a memory update. Although memory for the updated information was similar for both vehicle and RGFP966 mice, memory for the original training information was impaired by RGFP966 injection, indicating that there may be competition between the original memory and the updated information. For aging mice, post-update RGFP966 infusion ameliorated age-related impairments in memory updating without disrupting memory for the original training information. Together, these results indicate that HDAC3 plays a key role in memory updating in the young and aging brain. SUPPORT: K99/R00 AG056596, Penn State Biology Startup funding

Wright KM, Lee E, McDannald MA (*Boston College*) Roles for dorsal raphe/periaqueductal gray and retrorubral field dopamine in adaptive fear ABSTRACT: Fear in the face of certain threat is healthy and adaptive. However, equivalent levels of fear to uncertain threat and certain safety is maladaptive. Disruptions to brain regions underlying successful discrimination of danger and safety may have clinical implications in disordered fear. While considerable research has identified brain regions essential to acquiring fear to certain threats; neural circuits for adaptive fear across a range of uncertain threats are less understood. Dopamine (DA) is widely studied neuromodulator with distinct populations scattered throughout the midbrain. The ventral tegmental area and substantia nigra are canonical sources of midbrain dopamine. Yet many more dopamine populations exist. Here we investigated roles for noncanonical dorsal raphe/ventrolateral periaqueductal gray (vlPAG) and retrorubral field (RRF) dopamine in fear modulation. Male, Long Evans rats were given bilateral 6-hydroxydopamine (6-OHDA) depletions or sham procedures. Following recovery, rats received fear discrimination in which three auditory cues predicted unique foot shock probabilities: danger (p = 1.00), uncertainty (p = 0.25) and safety (p = 0.00). Control rats with DA intact demonstrated excellent discrimination to each of the three cues: high fear to danger, intermediate to uncertainty and low to safety. Depleting vlPAG DA disrupted overall fear discrimination while depleting A8 DA disrupted the temporal emergence of discrimination over cue presentation. The results reveal distinct, but essential roles for vlPAG and RRF DA in adaptive fear.

Yin XM, Chen S (*University of Ottawa*) Dissecting Neural Circuits Underlying Delayed Motor Learning in the 16p11.2 Dele-

tion Mouse Model of Autism ABSTRACT: The Autism Spectrum Disorders (ASDs) is a cluster of neurodevelopmental disorders that are often characterized by communication deficits, social interaction impairment, and stereotypic behaviors. Despite the common prevalence of this disorder, many studies also report ASD patients exhibit motor deficits and clumsiness. However, the neuronal pathophysiology underlying these motor symptoms remains elusive. The 16p11.2 chromosomal copy number deletion accounts for approximately 1% of ASD cases in humans. A homologous chromosome region, 7qF3, was identified in mice, and deletion of this chromosomal region has shown behavioral resemblance to the human disorder. We developed a novel motor task to train 16p11.2+/- mice on a head-fixed running apparatus. Interestingly, we did not find any motor coordination deficits in the 16p11.2+/- mice but they exhibited delayed learning compared to wild-type mice. To examine whether there are structural and functional abnormalities in the layer 2/3 (L2/3) neurons in 16p11.2+/-mice, we utilized in vivo two-photon imaging to chronically monitor dendritic spines and neuronal ensemble activity of L2/3 neurons in the primary motor cortex during learning. Our preliminary data suggest that 16p11.2+/- mice show a similar rate of learning-induced spine formation but these spines undergo a delayed pruning process. At the network level, we observe distinct, highly synchronous subpopulations of L2/3 excitatory neurons in the 16p11.2+/- mice that are highly selective to firing during specific behavioral states. Lastly, we observed fewer noradrenaline (NA) neurons in the locus coeruleus (LC) were activated during motor learning in the 16p11.2+/- mice. Pharmacogenetically stimulating NA neurons in the locus coeruleus, using the DREADDs system, during motor learning in the DBH-CreERT2::16p11.2+/- mice rescued the delay in spine elimination and improved the delayed motor learning. These findings demonstrate, for the first time, a dysfunctional LC-NA system that is accompanied by deficits in synaptic reorganization, ensemble activity patterns, and delayed motor learning in a mouse model of autism.

Yousuf H, Moyer JR (*University of Wisconsin - Milwaukee*) Intrinsic excitability of retrosplenial cortical neurons varies as a function of sex and age ABSTRACT: The granular retrosplenial cortex (gRSC) forms reciprocal connections with the hippocampus (Van Groen & Wyss, 2003). In rats, the gRSC is well-positioned to contribute to spatial learning and associative fear memories (Vann et al., 2009; Kwapis et al., 2015). Furthermore, previous studies have demonstrated sex differences in associative fear learning (Dalla et al., 2009), however, the extent to which sex differences in the electrophysiological properties of gRSC neurons contributes to these differences remains unknown. Despite its role in complex forms of memory, little is known about the intrinsic membrane properties of gRSC neurons, and nothing is known about how they vary as a function of sex. Using visually-guided, patch-clamp recordings in brain slices, we studied the intrinsic excitability of gRSC neurons as a function of developmental age and sex. We characterized a distinctive population of pyramidal neurons in L5 from both adult females and adult males. The majority of pyramidal neurons in L5 of the gRSC in both sexes have a prominent afterdepolarization (ADP) following a single spike and these neurons are characterized as regular-spiking ADP neurons (RSADP). Interestingly, RSADP neurons in L5 of gRSC from male rats exhibited an enhanced intrinsic excitability compared with those from female rats. For example, RSADP neurons from adult males had a lower action potential threshold and a reduced fast afterhyperpolarization (fAHP) compared to those from the adult female. Stark differences in the electrophysiological properties of gRSC neurons were also observed during development. For example, unlike adult neurons, the majority of recordings from male rats between postnatal days 14-29 indicate that those L5 pyramidal neurons do not have a prominent ADP, and are thus characterized as regular spiking (RS) neurons. In addition, their properties differ from those of adult male RS neurons, which have significantly higher neuronal excitability, a more depolarized resting membrane potential, a reduced action potential half-width, and a reduced fAHP. Exactly when during development, gRSC neurons in L5 shift from the classic RS property to the RSADP firing property observed in adults, and whether this varies with sex is currently unknown. These results demonstrate that the gRSC is a sexually dimorphic region that may contribute to observed sex differences in fear memories. Our studies also suggest that neurons within gRSC are physiologically dynamic during development and thus may play a critical role in emotional development.

Yu AJ, Ardiel EL, Rankin CH (*The University of British Columbia*) Neuropeptides differentially mediate sensitization and dishabituation of distinct response components. ABSTRACT: Sensitization and dishabituation are two forms of non-associative learning produced by a novel or noxious stimulus, that increase the likelihood and/or magnitude of a response. Although these two forms of non-associative learning have similar behavioural effects, previous research on Aplysia suggests that they emerge at different developmental stages and have nonidentical electrophysiological profiles. Research into the cellular and molecular mechanisms of sensitization and dishabituation can help to further distinguish the two forms of learning, and provide insight into the relationship between different forms of non-associative learning. Our studies found that neuropeptides differentially mediate sensitization and dishabituation. Using our high-throughput Multi-Worm Tracker in combination with optogenetics, we established paradigms for cross-modal sensitization and dishabituation. We identified a FLP-20/FRPR-3 peptidergic signalling pathway that specifically mediate tap-induced ASH response sensitization but not dishabituation. The PDF neuropeptide system mediates sensitization of a single response component, but not others. Taken together, our data suggest that a number of neuropeptide systems underlie different forms of non-associative learning, and that within a form of non-associative learning, several aspects of a single response can also be mediated by different neuropeptides. SUPPORT: NSERC

Zelikowsky M (*University of Utah*) "Stress-enhanced fear learning and violence" ABSTRACT: Models of post-traumatic stress disorder (PTSD) such as stress-enhanced fear learning (SEFL) have typically focused on the effects of trauma on subsequent fear, anxiety, and depression. Relatively few studies examine the effects of trauma on subsequent social behavior. In a mouse model of SEFL, we show that following trauma, mice show an enhancement in aggression and altered mating behavior. Subsequent machine vision and computational analyses reveals that the nature of this aggression is not only enhanced compared to controls but

also distinct in its nature. Consistent with a role for the neuropeptide Tac2 in fear and chronic social isolation stress, we found that chemogenetic and optogenetic perturbations of Tac2+ cells in the dBNST attenuated the effect of trauma to enhance aggression. Collectively, these data identify Tac2 as an important mediator of various forms of stress.

Zhang TR, Guilherme E, Kesici A, Vila-Rodriguez F, Snyder JS (*University of British Columbia*) Acute neurostimulation effects on hippocampal neurogenesis ABSTRACT: The neurogenic theory of electroconvulsive therapy (ECT) states that the induction of hippocampal neurogenesis is one of the biological mechanisms responsible for ECT's antidepressant effects. Hippocampal neurogenesis has been shown to be required for antidepressant effect, is negatively regulated by stress, and electroconvulsive stimulation very potently increases neurogenesis. To confirm and further elucidate specific changes in hippocampal neurogenesis, we stimulated mice with one session of electroconvulsive shock (ECS), the animal model of electrostimulation therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or intermittent theta burst stimulation (iTBS). In mice, we used bromodeoxyuridine (BrdU) to label neurons born two days prior to a single ECS, rTMS or iTBS treatment. Numbers of surviving BrdU+ cells, and proliferating PCNA+ cells, were examined 1, 3, and 7 days following neurostimulation. We found that just one session of ECS increased the number of BrdU positive cells significantly immediately starting on day 1, declining back to baseline on day 3. Proliferating PCNA+ cell levels were similar to shams on day 1, peaked on day 3, and declined to basal levels on day 7. In contrast, rTMS had no effect on levels of neurogenesis across time, suggesting that it does not exert its effects through neurogenesis. Finally, iTBS immediately increased neurogenesis but the number of newborn cells declined over 7 days to levels comparable to sham and rTMS animals. Collectively, we found that ECS had the most enhancements on hippocampal neurogenesis markers, iTBS had some moderate effect on increasing new-born neuron survival, and rTMS had no effect on neurogenesis.

9th Annual Women in Learning Luncheon Directions

Join WIL at TAPshack from 12 pm – 1:30 pm on Saturday, October 5th to hear from Dr. Sheena Josselyn about life, science, and academia.

TAPshack Coal Harbour address: 1199 Cordova St, Vancouver, BC V6E 4R5

Directions to TAPshack Coal Harbour from Coastal Coal Harbour Hotel (~3 min walk):

1. Head northwest on W. Hastings St. toward Bute St. (50m)
2. Turn right onto Bute St. (70m)
3. Cross over W. Cordova St. and enter Harbour Green Park. The restaurant is on the seawall, adjacent to a large stone staircase. (50m)