IBNS
International Behavioral Neuroscience Society

Annual Meeting Program and Abstracts

Boca Raton, Florida, USA
June 27-July 2, 2018

Abstracts of the 27th Annual Meeting of the International Behavioral Neuroscience Society

Volume 27, June 2018

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PRESIDENTIAL WELCOME

F. Scott Hall, PhD
IBNS President
Department of Pharmacology and Experimental Therapeutics
University of Toledo College of Pharmacy and Pharmaceutical Sciences
Toledo, Ohio, USA

Dear Friends and Colleagues,

I am delighted to welcome you to the 27th Annual Meeting of the International Behavioral Neuroscience Society (IBNS). As you are no doubt aware, the meeting had been originally planned for Puerto Rico, which continues to recover from the devastating consequences of Hurricane Maria. Even now, so long after the event, the Island is struggling to recover, and estimates of the full toll of the disaster continue to climb. We continue to ask all our members to reach out to colleagues in Puerto Rico, and to the community at large, and to help where you can. We were very fortunate to have support from Plexon and Thorlabs, who made contributions allowing 5 deserving students from Puerto Rico to attend the IBNS meeting this year. We thank them very much for their generosity that has benefited these deserving students.

After it became clear that we would have to move the location of the meeting, we were quite lucky to be able to hold the meeting in beautiful Boca Raton, Florida, but not without herculean efforts on the part of the IBNS staff, the IBNS Executive Director Marianne Van Wagner and our Business and Event Manager, Eve Van Wagner. This meeting could not have happened, and indeed our Society would not have continued to exist, without their steadfast loyalty and long-standing contributions to the Society. I extend to them our deepest thanks.

I would also like to thank our plenary speakers for being so helpful and accommodating with the change in venue. Much effort had originally gone into plans for Puerto Rico, so I would like to thank the original local organizing committee (LOC) from Puerto Rico (Carmen Maldonado-Vlaar, Arlene Martinez, Yancy Ferrer-Acosta, Carlos, Bolanos and Dinah Ramos-Ortolaza) for their hard work. I would especially like to thank a late addition to the LOC from Florida, Marcelo Febo, for his help and advice after the meeting had been moved to Florida.

Putting on a meeting like this requires a great deal of work from many people. The program this year has been enlarged and enriched, with 3 simultaneous symposia, and more presentations than at any previous IBNS meeting. This could not have happened without tremendous (and time-consuming) efforts from the Program Committee and its Chair, Elena Choleris, and Co-Chair, Farida Sohrabji. This year IBNS also gave away more student and post-doctoral travel awards than ever before, to a very impressive group of young scientists. We are appreciative of their work and efforts and will show-case their work, as always, in the Travel Award Blitz. Choosing the award winners from among the accomplished applicants was the very difficult work of the Education and Training Committee, and its Chair, Stacey Sukoff Rizzo, and Co-Chair, Corina Bondi. We thank them all for their diligence, time and hard work. Lastly, I wish to acknowledge our student representative, Cindy Barha, for her numerous contributions to the meeting.

IBNS is also exceedingly thankful for the support of its sponsors. First and foremost among this group is the long-standing and continuing support of Elsevier Science, the publisher of our official journals, *Neuroscience & Biobehavioral Reviews* and *Pharmacology, Biochemistry and Behavior*, who will once again hold a lunchtime seminar on scientific publishing. We would also like to recognize our major sponsors Plexon, Thorlabs, Stoelting, Harvard Bioscience, and Noldus for their support of the meeting. Noldus has also helped to organize and sponsor, with Past-President Robert Gerlai, a lunchtime workshop on Zebrafish methods, and we are very appreciative of their efforts. We are thankful to all our sponsors and exhibitors and encourage you to visit their booths during the breaks at the conference to discuss your research needs.

I am looking forward to another outstanding meeting in Boca Raton, Florida.

Best wishes,

F. Scott Hall
President, IBNS

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Europe..... Benoit Martin
Europe.....Davide Amato
Latin America ..... Ana Lucia Rodrigues
Student ..... Cindy Barha
USA..... Jill Silverman
USA.....Charles Heyser
USA..... Susanne Brummelte

AWARDS

Outstanding Career Award. The 2018 Outstanding Career Award will be presented to Kelly Lambert. She will be presenting her award talk entitled *The Snark was a Boojum: Reconsideration in the context of Behavioral Neuroscience*, on Thursday, 7:00 p.m. She will be presented with a plaque during the IBNS Awards banquet on Sunday evening.

Dr. Lambert is a Past-President (2009-2011) of IBNS. Her contributions to IBNS, to education of students, and to the field of behavioral neuroscience make her exceptionally deserving of this the Outstanding Career Award. Dr. Lambert recently moved to the University of Richmond where she became Professor of Behavioral Neuroscience in the Department of Psychology, from Randolph-Macon College, where she was the Macon and Joan Brock Professor and Chair of Psychology. Her research interests have been diverse, leading her to study species from deer mice to owl monkeys. Although she has contributed research in many areas of behavioral neuroscience, her best-known work has focused on aspects of maternal behavior, paternal behavior, neuroplasticity, and emotional resilience. Her work has demonstrated how the experience of parenting affects stress-resilience, coping, aspects of cognitive function, and many other behaviors critical to the survival of the organism. This work has been exceptionally creative and has repeatedly captured the minds of young researchers as well as the general public. As an example of this creativity, although environmental enrichment has long been known to affect behavior and brain function, Dr. Lambert and her colleagues demonstrated that "naturalistic" enrichment has much greater effects than traditional enrichment approaches on behavioral, neuroendocrine, and brain functions [as described in *Brains in the City*, a review article (*Neuroscience and Biobehavioral Reviews*, 2015) based on a previous IBNS symposium]. Dr. Lambert is also an accomplished and recognized educator and mentor. She has received numerous teaching awards, including the 2008 Virginia Professor of the Year and the Mary Erskine Award for Mentoring in Behavioral Neuroscience, among others. She has also published two major textbooks: *Clinical Neuroscience: The neurobiological foundations of mental health and Biological Psychology*. Dr. Lambert's work has also been very well received by the general public and was recently featured on *CBS Sunday Morning*. Her popular science articles include writing on the maternal brain and stress-resilience, and also how undergraduate students contributed to her research. She has written two popular books, *Lifting Depression: A neuroscientist's hands-on approach to activating your brain's healing power* (also translated into Japanese) and *The Lab Rat Chronicles: A neuroscientist reveals life lessons from the planet's most successful mammals* (also translated to German). Her most recent book *Well-Grounded: The neurobiology of rational decisions* (Yale University Press) will be released this September.

Early Career Achievement Award. The 2018 Early Career Achievement Award will be presented to Cindy Barha during the IBNS Awards Banquet. Cindy will receive $500, a waiver for registration fees and will give a talk entitled *Biological sex and parity: Potential moderators of exercise efficacy on brain health* on Thursday, 6:30 p.m.

Dr. Barha is a postdoctoral fellow in the Aging, Mobility, and Cognitive Neuroscience Laboratory led by Professor Teresa Liu-Ambrose, in the Department of Physical Therapy, Faculty of Medicine, at the University of British Columbia (UBC). Dr. Barha received her PhD in 2013 in Behavioral Neuroscience from UBC, where she worked with Dr. Liisa Galea. Although still a postdoctoral fellow, Dr. Barha has published 28 papers (17 as first author). Her work has received both scientific acclaim and public attention, including her recent work showing that increased parity is associated with longer telomeres, a potential biomarker of biological aging. Her transdisciplinary and translational research investigates the interactions between the brain, physical health, and mental health to determine the neurobiological substrates mediating these relationships, and how biological sex affects brain aging and brain health. Dr. Barha's research thus addresses major societal and health care issues (i.e., brain health and dementia). Dr. Barha's research excellence has been consistently recognized nationally and internationally: Including a prestigious 3-year research fellowship from the Alzheimer's Association (USA); postdoctoral fellowships from the Canadian Institutes of Health Research (CIHR) and the Michael Smith Foundation for Health Research; the Servier Young Investigator Award; and the CIHR Institute of Aging Age+ Prize. Her PhD thesis won the British Columbia Psychological Association Graduate Gold Medal in Psychology and the Canadian Psychological Association 2013 Certificate of Academic Excellence for Doctoral Thesis. Dr. Barha has been a very active member of IBNS and is currently the IBNS student representative to Council.

TRAVEL AWARDS

We are pleased to announce the recipients of the IBNS Travel Awards for the 2018 meeting in Boca Raton, USA. Award winners will receive a cash award, certificate, and waiver of registration fees. Travel awardees are presenting orally and will also have their research presented in a poster session. Congratulations to all. Funding for the travel awards has been provided by the generosity of our sponsors Elsevier Science, Plexon, ThorLabs and the IBNS members.

2018 Travel Award Recipients *(listed alphabetically)*

Postdoctoral Travel Awards

Fernando Caravaggio, University of Toronto, Toronto, ON, Canada
Patricia B. de la Tremblaye, University of Pittsburgh, Pittsburgh, PA, USA
Jessica Deslauriers, University of California San Diego, La Jolla, CA, USA
Maria Diehl, University of Puerto Rico School of Medicine, San Juan, PR, USA
Anand Gururajan, University College Cork, Cork, Ireland
Joshua Haight, Yale University, New Haven, CT, USA

Graduate Student Travel Awards

Hector Bravo-Rivera, University of Puerto Rico, San Juan, PR, USA
Chelsea Brown, UCSB, Santa Barbara, CA, USA
Caitlin Burgdorf, Weill Cornell Medicine, New York, NY, USA
Courtney Bryce, University of British Columbia, Vancouver, BC, Canada
Nicholas Everett, Macquarie University, Marsfield, NSW, Australia
Niveen Fulcher, University of Western Ontario, London, ON, Canada
Lina Fernanda Gonzalez Martinez, University of Texas, Austin, TX, USA
Caesar Miguel Hernandez, University of Florida, Gainesville, FL, USA
Sofiya Hupalo, University of Wisconsin, Madison, WI, USA
Rukhshona Kayumova, Philipps University, Marburg, Germany
Brittany Kuhn, University of Michigan, Ann Arbor, MI, USA
Jennifer Martin, State University of New York, Buffalo, NY USA
Solianne Martinez-Jimenez, Universidad Central del Caribe, Bayamon, PR, USA
Laura Mendez, University of Puerto Rico, Medical Sciences Campus, San Juan, PR, USA
Kelly Moench, Indiana University, Bloomington, IN, USA
Shin Park, University of Florida, Gainesville, FL, USA
Jacqueline Quigley, University of Michigan, Ann Arbor, MI, USA
Melissa Rivera-Lopez, University of Puerto Rico School of Medicine, San Juan, PR, USA
Luan Tonelli, Philipps University, Marburg, Germany
Margarida Trigo, University of Manchester, Manchester, United Kingdom
Katie E. Yoest, University of Michigan, Ann Arbor, MI, USA
Sean Shenghua Zhu, University of Manitoba, MB, Canada (2017 Award)

Undergraduate Student Travel Awards

Dmitry S. Kovalev, University of Richmond, Richmond, VA, USA
Ben Tsang, University of Toronto, Mississauga, ON, Canada

Presidential Travel Award

Amanda Facciol, University of Toronto, ON, Canada

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The IBNS would like to express our gratitude to the following organizations that have given financial support to the 27th International Behavioral Neuroscience Society Conference.

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Please take time to visit the exhibit tables and thank these companies for their support.

ACKNOWLEDGMENTS

The Society would like to extend our deep appreciation to the following committees that are responsible for the success of this meeting:

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Julianne Jett
Jill McGaughy
Verity Brown
Christie Pizzimenti
Corina Bondi
Kelly Lambert
Mumeko Tsuda
Peter Kalivas
Cindy Barha

Any IBNS member who would like to become more involved in the Society may volunteer to serve on an IBNS committee. Committee details can be found on our website at:
http://www.ibnsconnect.org/committees

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Manuel Diaz, University of Puerto Rico Medical Sciences Campus
Marcelo Febo, University of Florida

REGISTRATION: Please pick up your name badge during the opening Reception on Wednesday, 6:00-8:00 p.m., Cathedral Room. There is no on-site registration – ALL registrations must be made online, prior to the start of the meeting. Name badges are required for ALL events, including the opening reception and closing banquet – no exceptions. There will be a $10 fee for replacement badges. You may also pick up your badge prior to morning sessions each day.

PROGRAM

Wednesday, June 27

4:00-6:00 Student/Post-Doc Social. *Location TBA*

6:00-8:00 Regiception – Welcome Reception and Registration. *Cathedral Room*

Thursday, June 28

8:00-9:00 **Presidential Lecture: Avoiding danger at all costs.**
Quirk, Gregory J., University of Puerto Rico School of Medicine, Puerto Rico, USA. *Great Hall South*

9:00-9:30 **Refreshment Break – Exhibits.** *Camino Hall*

9:30-11:30 **Symposium: Social neuroscience in rodents: Neural foundations and clinical implications.** Chair: Markus Wöhr, Philipps University of Marburg. Co-Chair: Jill L. Silverman, University of California Davis. *Great Hall North*

- 9:30-9:54 **Rodent ultrasonic communication: Brain and behavior.**
  Wöhr, Markus
- 9:54-10:18 **Developmental social communication in two genetic rat models of neurodevelopmental disorders.**
  Berg, Elizabeth L.; Wöhr, Markus; Silverman, Jill L.
- 10:18-10:42 **Time-scales of auditory cortical neurons for coding and classifying timing cues found in non-speech vocalizations.**
  Read, Heather L.; Escabi, Monty A.
- 10:42-11:06 **Social decision making in rats.**
  van Wingerden, Marijn; van Berkel, Mireille; van Gurp, Sander; Seidisarouei, Mohammad
- 11:06-11:30 **Glutamatergic mechanisms in the inferior colliculus play a key role in paradoxical kinesia induced by appetitive 50-kHz ultrasonic vocalisations in rats.**
  Tonelli, Luan; Wöhr, Markus; Schwarting, Rainer; Melo-Thomas, Liana

9:30-11:30 **Symposium: Optimizing brain performance: Identifying mechanisms of adaptive neurobiological plasticity.** Chair: Kelly Lambert, University of Richmond. *Great Hall South*

9:30-10:00 **Maximizing neurobiological affordances via fine-tuned response-outcome contingencies.**
Lambert, Kelly

10:00-10:30 **Is More Always Better? Optimizing performance with hippocampal neuroplasticity in males and females.** Galea, Liisa A.M.; Yagi, Shunya

10:30-11:00 **Crossing the memory-mood divide: stimulation of entorhinal cortex-dentate gyrus circuitry is antidepressive and improves memory in mice.**
Eisch, Amelia; Yun, Sanghee

11:00-11:30 **Growing your neurological (cognitive) reserve.**
Merzenich, Michael

9:30-11:00 **Symposium: Neural circuit mechanisms of mouse behavior.** Chair: Yi Zuo, University of California, Santa Cruz. Co-Chair: Ju Lu, University of California, Santa Cruz. *Granada ABC*

9:30-10:00 **Stress induces synaptic and circuit reorganization in the mouse cerebral cortex.**
Chen, Chia-Chien; Lu, Ju; Yang, Renzhi; Ding, Jun B.; Zuo, Yi

10:00-10:30 **Noradrenergic modulation of sensory processing in the mouse tactile system.**
Yang, Hongdian; Bari, Bilal A.; Cohen, Jeremiah Y.; O'Connor, Daniel H.

10:30-11:00 **Functional diversity of new spines formed during a forelimb-specific reaching task.**
Lu, Ju; Ma, Shaorong; Zuo, Yi

11:30-1:30 **Lunch Break** (lunch is not provided)

11:30-1:30 **Workshop:** After attending this free workshop, one in the Elsevier Publishing Connect Workshop series, early career researchers will be given an idea of the steps required to be taken before starting to write a paper. They will also be able to plan writing manuscripts using the logical step sequence – not the sequence in which the paper will be read. Authors are also made aware of what aspects of their papers Editors, Reviewers, and Publishers look at critically, and can ensure that in taking care of these areas, their papers are more likely to be accepted. Sensitive areas such as publishing ethics, plagiarism, duplicate publishing, etc. are also explained such that participants have an understanding of what their responsibilities are, what is allowed, and what is not permitted. At least two Editors of Elsevier journals will also be on hand to answer questions. *Great Hall North*

1:30-3:30 **Symposium: Environment and the epigenome: How experience contributes to psychiatric illness.** Chair: Zackary A. Cope, University of California, San Diego. Co-Chair: Jared W. Young, University of California, San Diego. *Great Hall South*

1:30-2:00 **How are maternal-derived signals converted into enduring epigenetic processes in the developing brain?**
Baram, Tallie Z.; Short, Annabel K.; Bolton, Jessica L.

2:00-2:30 **Winter-like photoperiods induce psychiatry-relevant behaviors in mice: Evidence for resiliency in mice with reduced dopamine transporter expression.**
Cope, Zackary A.; Kwiatkowski, Molly; van de Chappelle, Chuck; Lavadia, Maria L.; Dulcis, Davide; Young, Jared W.

2:30-3:00 **Preconception opioid exposure has bidirectional effects on morphine and cocaine reward in offspring.**
Vassoler, Fair; Toorie, Anika; Teceno, Delaney; Patton, Trevor; Byrnes, Elizabeth

3:00-3:30 **Transcriptional corepressor complexes in the regulation of neuronal plasticity.**
Telese, Francesca; Perez, Patricia Montilla; Florio, Ermanno; Lemolo, Attilio; Qi, Ma; Rosenfeld, Michael G.; Wen, Junneng; Rusu, Iulia

1:30-3:30 **Symposium: The new kid on the block: Astrocytes in behavior and cognition.** Chair: Mikhail V. Pletnikov, Johns Hopkins University School of Medicine. Co-Chair: Kathryn J. Reissner, University of North Carolina at Chapel Hill. *Great Hall North*

1:30-2:00 **Cells that tile your brain: Astrocyte roles in neural circuits.**
Khakh, Baljit S.

2:00-2:30 **Experience-dependent plasticity of astrocytes within the reward circuitry.**
Testen, Anze; Healey, Kati L.; Sepulveda-Orengo, Marian T.; Reissner, Kathryn J.

2:30-3:00 **Astroglial MHCI following immune activation leads to behavioral and neuropathological changes.**
Yamada, Kiyofumi; Sobue, Akira; Ito, Norimichi; Nagai, Taku

3:00-3:30 **The region-specific role of astrocyte DISC1 in cognitive behaviors in mice.**
Terrillion, Chantelle E.; Crawford, Joshua A.; Shevelkin, Alex; Kim, Sun-Hong; Fukudome, Daisuke; Sawa, Akira; Kamiya, Atsushi; Pletnikov, Mikhail V.

1:30-3:30 **Symposium: Corticotropin-releasing factor (CRF) modulation of cognition and motivation.** Chair: Sofiya Hupalo, University of Wisconsin, Madison. Co-Chair: Stan Floresco, University of British Columbia. *Granada ABC*

1:30-2:00 **Corticotropin-releasing factor and stress affect cognitive flexibility through biogenic amine systems.**
Valentino, Rita

2:00-2:30 **Corticotropin-Releasing Factor (CRF) modulation of different forms of cost/benefit decision making.**
Floresco, Stan

2:30-3:00 **Sex differences in stress responses: A critical role for corticotropin releasing factor.**
Bangasser, Debra

3:00-3:30 **Corticotropin-Releasing Factor (CRF) modulation of distinct prefrontal cortex (PFC)-dependent cognitive processes.**
Hupalo, Sofiya.

3:30-4:00 **Refreshment Break – Exhibits.** *Camino Hall*

4:00-6:00 **Travel Award Blitz – Co-Chairs:** Stacey Rizzo, The Jackson Laboratory. Jill Silverman, MIND Institute, UC Davis School of Medicine. *Great Hall South*

4:00-4:02 **Introduction.**

Undergraduate Student Travel Awards

4:02-4:06 **Tracking the impact of early-life challenges on neurobiological correlates of social and stress responses in female adult rats.**
Kovalev, Dmitry; Brooks, Milan; Kent, Molly; Lambert, Kelly

4:06-4:10 **Zebrafish responds to alcohol in the water before it reaches its brain.**
Tsang, Benjamin; Tran, Steven; Chow, Hayden; Gerlai, Robert

Graduate Student Travel Awards

4:10-4:14 **Managing threat-reward conflict: Strategies of conflict-based decision making.**
Bravo-Rivera, Hector; Rubio-Arzola, Patricia; Rodriguez-Aquino, Paula; Caban-Murillo, Albit; Quirk, Gregory

4:14-4:18 **Localizing the role of Homer2 in regulation of methamphetamine reinforcement.**
Brown, Chelsea; Fultz, Elissa; Ferdousian, Sami; Rogers, Sarina; Lustig, Eli; Kippin, Tod; Szumlinski, Karen

4:18-4:22 **Hippocampal Cav1.2 channels mediate extinction of cocaine-associated memories via dopamine D1R activation.**
Burgdorf, Caitlin E.; Fischer, Delaney; Bavley, Charlotte C.; Martinez-Rivera, Arlene; Hackett, Jonathan; Rajadhyaksha, Anjali M.

4:22-4:26 **The role of corticotropin-releasing factor in depressive-like behavior under conditions of uncertainty.**
Bryce, Courtney A.; Adalbert, Alexandra J.; Claes, Mona M.; Floresco, Stan B.

4:26-4:30 ~~**Oxytocin in the prelimbic cortex reduces cue- and drug-induced reinstatement of methamphetamine seeking behaviours.**~~
~~Everett, Nicholas; Baracz, Sarah; Cornish, Jennifer.~~ *Unable to attend.*

4:30-4:34 **Effect of DREADD-induced inhibition of cholinergic, glutamatergic and all PPTg neurons on sensorimotor gating.**
Fulcher, Niveen; Azzopardi, Erin; De Oliveira, Cleusa; Schmid, Susanne.

4:34-4:38 **Stress during puberty has differential effects on impulse action and introduction of delays in reward contingencies.**
Gonzalez-Martinez, Lina Fernanda; Lee, HongJoo Joanne; Delville, Yvon.

4:38-4:42 **Optogenetic inactivation of basolateral amygdala in young rats recapitulates aged rats' ability to delay gratification in an intertemporal choice task.**
Hernandez, Caesar M.; Orsini, Caitlin A.; McQuail, Joseph A.; Bruner, Matt M.; Labiste, Chase; Wheeler, Alexa-Rae; Ten Eyck, Tyler W.; Singhal, Sarthak; Burke, Sara N.; Frazier, C. Jason; Setlow, Barry; Bizon, Jennifer L.

4:42-4:46 **Corticotropin-Releasing Factor (CRF) modulation of distinct prefrontal cortex (PFC)-dependent cognitive processes.**
Hupalo, Sofiya.

4:46-4:50 **Altered emission of isolation-induced ultrasonic vocalizations in Cacna1c haploinsufficient rat pups.**
Kayumova, Rukhshona; Kisko, Theresa M.; Braun, Moria D.; Schwarting, Rainer K.W.; Wöhr, Markus

4:50-4:54 **The effects of chemogenetic inhibition of prelimbic cortical inputs to the paraventricular nucleus of the thalamus on cue- and cocaine-induced drug-seeking behavior in sign-trackers vs. goal-trackers.**
Kuhn, Brittany; Campus, Paolo; Klumpner, Marin; Flagel, Shelly

4:54-4:58 **Drebrin regulates opiate-induced behavioral and structural plasticity in the Nac.**
Martin, Jennifer; Werner, Craig; Zhong, Ping; Wang, Zi-Jun; Siemian, Justin; Hagarty, Devin; Neve, Rachael; Li, Jun-Xu; Chandra, Ramesh; Lobo, Mary-Kay; Gancarz, Amy; Yan, Zhen; Dietz, David

4:58-5:02 **A single injection of losartan improves neurological outcome in male and female rats subjected to ischemic stroke.**
Martinez-Jimenez, Solianne; Gonzalez-Vega, Maxine, Ferchmin, Pedro; Martins, Antonio.

5:02-5:06 **The modulatory effect of rosmarinic acid in the rhythmic motor patterns of the lumbar spinal cord of neonatal mice.**
Mendez, Laura; De Jesus, Kevin; Garcia, Andrea; Diaz, Manuel

5:06-5:10 **Sex-dependent effects of two-hit stress on behavioral flexibility in rodents.**
Moench, Kelly M.; Wellman, Cara L.

5:10-5:14 **Musical pleasure affects forward gait in patients with Parkinson's disease.**
Park, K. Shin; Hass, Chris J.; Patel, Bhavana; Janelle, Christopher M.

5:14-5:18 **Effects of ICI 182,780 on preference for cocaine in male rats .**
Quigley, Jacqueline; Lalani, Lahin; Lipkin, Benjamin; Becker, Jill.

5:18-5:22 **Effects of experimental concussion by closed head injury on conditioned fear in rats.**
Rivera-Lopez, Melissa; Sierra-Mercado, Demetrio

5:22-5:26 **Glutamatergic mechanisms in the inferior colliculus play a key role in paradoxical kinesia induced by appetitive 50-kHz ultrasonic vocalisations in rats.**
Tonelli, Luan; Wöhr, Markus; Schwarting, Rainer; Melo-Thomas, Liana

5:26-5:30 **Relational memory in the scPCP mouse model for schizophrenia.**
Trigo, Margarida; Silverman, Jill; Neill, Joanna; Gigg, John

5:30-5:34 **Gonadal hormones mediate changes in adaptive choice and dopamine release in female rats.**
Yoest, Katie E.; Shashlo Kelly E.; Cummings, Jennifer A.; Becker, Jill B.

5:34-5:38 **Role of neuroinflammation and amyloid in cognitive impairment in a mouse model of Alzheimer's disease.**
Zhu, Shenghua; Wang, Jun-Feng; Li, Xin-Min.

Postdoctoral Travel Awards

5:38-5:42 **Reward motivation in humans and its relationship to dopamine D2/3 receptor availability: A pilot study with dual [11C]-raclopride and [11C]-(+)-PHNO imaging.**
Caravaggio, Fernando; Fervaha, Gagan; Browne, Caleb; Gerretsen, Philip; Remington, Gary, Graff-Guerrero, Ariel

5:42-5:46 **Role of Cannabinoid CB1 receptors in mediating the long-term effects of adolescent chronic stress on the behavioral impairments following traumatic brain injury in adult rats**
de la Tremblaye, Patricia; Wellcome, Jody; Wiley, Kaitlyn; Cheng, Jeffrey; Bondi, Corina, Kline, Anthony

5:46-5:50 **COMTval158met polymorphism-modulated response to LPS is regulated through dopamine D1 signaling pathway: A first study linking COMTval158met polymorphism and immune mechanisms.**
Deslauriers, Jessica; Zhou, Xianjin; Risbrough, Victoria.

5:50-5:54 **Prefrontal function in fear and avoidance: From reaction to action.**
Diehl, Maria M.; Bravo-Rivera, Christian; Rodriguez-Romaguera, Jose; Pagan-Rivera, Pablo; Burgos-Robles, Anthony; Roman-Ortiz, Ciorana; Iravedra-Garcia, Jorge; Gonzalez-Diaz, Fabiola; Quirk, Gregory J.

5:54-5:58 **Stress resilience: A state of mind, a state of gut.**
Gururajan, Anand; Ventura-Silva, Ana-Paula; Lyte, Joshy; Becker, Thorsten; Van de Wouw, Marcel; Boehme, Marcus; Mercx, Barbara; Wiley, Niamh; Moloney, Gerard; Stanton, Catherine; Dinan, Timothy; Cryan, John

5:58-6:02 **Acetylcholine signaling in the ventral tegmental area regulates motivation to work for a desirable reward in an effort-based decision-making task.**
Haight, Joshua; Rathi, Durga; Nunes, Eric; Addy, Nii.

6:00-6:30 **Break – Exhibits**

6:30-7:00 **Early Career Award: Biological sex and parity: Potential moderators of exercise efficacy on brain health.** *Great Hall South*
Barha, Cindy K.; Rosano, Caterina; Best, John R.; Liu-Ambrose, Teresa

7:00-7:30 **Outstanding Career Award: The Snark was a Boojum: Reconsideration in the context of Behavioral Neuroscience.** *Great Hall South*
Lambert, Kelly

Friday, June 29

8:00-9:00 **Keynote Speaker: Parental stress and epigenetic programming of offspring neurodevelopment.** Bale, Tracy L., University of Maryland School of Medicine, Baltimore, MD, USA. *Great Hall South*

9:00-9:30 **Refreshment Break – Exhibits.** *Camino Hall*

9:30-11:00 **Symposium: Modifiable Risk Factors Contributing to Age-Related Memory Loss.** Chair: Joseph A. McQuail, University of Florida, Gainesville. *Granada ABC*

- 9:30-10:00 **Influence of age- and stress-related neuroendocrine dysfunction on executive functions and synaptic markers in prefrontal cortex.** McQuail, Joseph A.
- 10:00-10:30 **Nutritional ketosis enhances cognitive resilience.** Hernandez, Abbi R.
- 10:30-11:00 **Systemic inflammation mediates age-related cognitive deficits.** Lin, Tian

9:30-11:30 **Symposium: Reactivation-induced memory destabilization: A gateway to memory change with significant therapeutic implications.** Chair: Boyer Winters, University of Guelph. *Great Hall North*

- 9:30-10:00 **Inducing prediction error to trigger reconsolidation.** Exton-McGuinness, Marc; Lee, Jonathan
- 10:00-10:30 **Retrieval-extinction without destabilisation still reduces recovery of fear.** Cahill, Emma N.; Wood, Melissa A.; Everitt, Barry J.; Milton, Amy L.
- 10:30-11:00 **Acetylcholine as a novel key to memory destabilisation: Implications for the updating of established memories in healthy and dysfunctional brains.** Winters, Boyer
- 11:00-11:30 **Modifying human episodic memories: reactivation as a precondition for change.** Hupbach, Almut; Scully, Iiona

9:30-11:30 **Symposium: Social transmission of information in mammals: Key insights from rodents and non-human primates.** Chair: Aleksandra Vicentic, National Institute of Mental Health. Co-Chair: Anthony Noel Burgos-Robles, Massachusetts Institute of Technology. *Great Hall South*

- 9:30-10:00 **Observational fear learning requires cortico-amygdala transfer of socially-derived information.** Burgos-Robles, Anthony; Allsop, Stephen; Wichmann, Romy; Mills, Fergil; Chang, Chia-Jung; Felix-Ortiz, Ada; Vienne, Alienor; Beyeler, Anna; Izadmehr, Ehsan; Glober, Gordon; Cum, Meghan; Stergiadou, Johanna; Anandalingam, Kavitha; Farris, Kathryn; Namburi,
- 10:00-10:30 **A putative role of the primate amygdala in the receiving-emitting cycle of facial expressions.** Gothard, Katalin M.; Zimmerman, Prisca E.; Morrow, Jeremiah Kegley; Fuglevand, Andrew J.

10:30-11:00 **Social dominance status predicts vicarious fear learning from conspecifics in rats.**
Monfils, Marie-H.; Jones, Carolyn E.

11:00-11:30 **Observational fear as an enhancer of inhibitory avoidance.**
Morozov, Alexei; Ito, Wataru.

11:30-1:30 **Lunch Break** (lunch is not provided)

11:30-1:30 **Noldus Workshop: Zebrafish-Based Models in Behavioral Neuroscience.** *Great Hall North*

Zebrafish (Danio rerio) are rapidly growing in popularity as a model in neuroscience, toxicology and behavioral research. The goal of this workshop is to demonstrate to the IBNS community the growing utility of zebrafish-based models in behavioral neuroscience. In addition, to the use of zebrafish in neurogenetics and neurodevelopmental research, both larval and adult zebrafish are gaining popularity in high-throughput drug screening, toxicological assays, as well as mimicking complex brain disorders. Noldus Information Technology will host this event and prepare a live demo of the software. Cold cut sandwiches, ice tea, coffee, water and a selection of cookies will be served.

11:30-11:45 **Opening: Behavioral Quantification**
Guidi, Michael

11:45-12:15 **Behavioral test paradigms (for adult zebrafish): How to mirror task, shoaling task and anxiety task.**
Tsang, Ben; Facciol, Amanda

12:15-12:30 **Zebrafish as an excellent research subject for behavioral neuroscience.**
Gerlai, Robert

12:30-1:30 **Questions and Answers.**

1:30-3:30 **Symposium: Mechanisms underlying memory consolidation and retrieval.** Chair: Ryan LaLumiere, University of Iowa. Co-Chair: Janine Kwapis, University of California, Irvine. *Great Hall North*

1:30-2:00 **Specific projections from the amygdala modulate the consolidation for different aspects of memory.**
LaLumiere, Ryan T.

2:00-2:30 **Epigenetic regulation of the circadian gene Period1 in the hippocampus mediates age-related changes in memory and synaptic plasticity.**
Kwapis, Janine; Alaghband, Yasaman; Kramar, Eniko; Lopez, Alberto; Vogel Ciernia, Annie; White, Andre; Shu, Guanhua; Rhee, Diane; Michael, Christina; Montellier, Emilie; Liu, Yu; Magnan, Christophe; Sassone-Corsi, Paolo; Baldi, Pierre; Matheos, Dina; Wood

2:30-3:00 **The modulatory role of the endocannabinoid system on the consolidation and retrieval of memory for stressful experiences in rats.**
Campolongo, Patrizia

3:00-3:30 **Molecular mechanisms of memory reconsolidation and strengthening.**
Alberini, Cristina M.

1:30-3:30 **Symposium: Developmental and experiential factors influencing alcohol's effects on the brain.** Chair: Cheryl McCormick, Brock University. *Great Hall South*

1:30-2:00 **Developmental ethanol and attention: Long-lasting dysregulation of attention performance and its underlying prefrontal circuitry.**
Louth, Emma; Luctkar, Hanna; Spatafora, Laura; Sutton, Charles; Taylor, Christine; Bailey, Craig

2:00-2:30 **Maternal care and sex differences in alcohol related behavior, anxiety and the brain.**
Cameron, Nicole M.

2:30-3:00 **Social instability stress and social context distinctly influence the intake of ethanol and sucrose.**
Marcolin, Marina L.; Hodges, Travis E.; Baumbach, Jennet L.; McCormick, Cheryl M.

3:00-3:30 **Embryonic alcohol exposure in zebrafish: Modeling the milder and more prevalent form of fetal alcohol spectrum disorders.**
Gerlai, Robert; Fernandes, Yohaan; Chatterjee, Diptendu; Buske, Christine; Mahabir, Samantha; Seguin, Diane

1:30-3:30 **Symposium: Inflammation in psychiatric disorders: What we know and what is next.** Chair: Atsushi Kamiya, Johns Hopkins University School of Medicine. Co-Chair: Juliet Richetto, University of Zürich. *Granada ABC*

1:30-2:00 **Sex differences in the immune response to stress.**
Hodes, Georgia

2:00-2:30 **Microglial inflammation for exploring novel pharmacological intervention of stress-induced psychiatric disorders.**
Kamiya, Atsushi

2:30-3:00 **Epigenetic and transgenerational effects of maternal immune activation.**
Richetto, Juliet; Weber-Stadlbauer, Ulrike; Meyer, Urs

3:00-3:30 **Adolescent cannabis exposure and astrocyte-specific genetic vulnerability synergistically activate inflammation signaling and affect cognition in adulthood.**
Pletnikov, Mikhail V.; Jouroukhin, Yan; Zhu, Xiaolei; Shevelkin, Alexey; Hasegawa, Yuto; Norris, Alexis L.; Abazyan, Bagrat; Saito, Atsushi; Pevsner, Jonathan; Kamiya, Atsushi

3:30-4:00 **Refreshment Break – Exhibits.** Camino Hall

4:00-6:00 **Symposium: The end of chronic stress, or is it?** Chair: Cheryl Conrad, Arizona State University. *Great Hall North*

4:00-4:30 **Animal model of anorexia nervosa: Behavioral, neurochemical and anatomical changes that persist beyond weight restoration.**
Aoki, Chiye; Chen, Evelyn Yi-Wen; Sherpa, Ang D.; Chowdhury, Tara G.; Wable, Gauri S.; Santiago, Adrienne N.

4:30-5:00 **Cortical integration of behavioral and physiological stress responses.**
Wallace, Tyler; Schaeuble, Derek; Pace, Sebastian; Herman, James P.; Myers, Brent

5:00-5:30 **Hippocampal mechanisms involved in the improvement from cognitive deficits following the end of chronic stress.**
Conrad, Cheryl D.; Ortiz, J. Bryce

5:30-6:00 **Sex differences in risk and resilience: Recovery of stress-induced dysfunction of prefrontal cortex in male and female rats.**
Moench, Kelly M.; Wellman, Cara L.

4:00-5:45 **Oral Session 1:** Chair: Michael Bowen, University of Sydney. *Granada ABC*

4:00-4:15 **High precision and transient stimulation from advanced automated laser tracking and optogenetic manipulation system (a-ALTOMS) manipulation neuronal circuit during operant restraining memory.**
Hsiao, Po-Yen; Wu, Ming-Chin; Lin, Yen-Yin; Chiang, Ann-Shyn

4:15-4:30 **Alleviating cognitive impairments in Mild Neurocognitive Disorder using transcranial infrared laser stimulation.** Alexander, Courtney; Saucedo, Celeste L.; Foret, Janelle T.; Barrett, Douglas W.; Haley, Andreana P.; Gonzalez-Lima, F.

4:30-4:45 **Infrared laser stimulation enhances sustained attention and working memory in mild neurocognitive impairment.**
Saucedo, Celeste L.; Alexander, Courtney; Barrett, Douglas W.; Gonzalez-Lima, F.

4:45-5:00 **Orphan receptor GPR158 controls stress-induced depression.**
Sutton, Laurie; Orlandi, Cesare; Martemyanov, Kirill

5:00-5:15 **Interrelationship between synaptic connectivity and neurocognitive impairments (NCI) in the HIV-1 transgenic rat.**
McLaurin, Kristen; Li, Hailong; Booze, Rosemarie; Mactutus, Charles

5:15-5:30 **Restoration of synaptic integrity and function following HIV-1 induced damage.**
Booze, Rosemarie; McLaurin, Kristen; Mactutus, Charles

5:30-5:45 **Modeling neuroHIV progression in the post-cART era.**
Mactutus, Charles F.; McLaurin, Kristen A.; Booze, Rosemarie M.

4:00-6:00 **Symposium: Cingulate cortex: The who, what and how of cognitive control.** Chair: Jill McGaughy, University of New Hampshire Durham, NH USA. Co-Chair: Emmanuel Procyk, Stem Cell and Brain Research Institute, University of Lyon, Lyon, France. *Great Hall South*

4:00-4:30 **Decoding predictions about the future in anterior cingulate cortex ensembles.**
Hyman, James M.

4:30-5:00 **Anterior cingulate cortex and cognitive control in the rat: Insights from chemo-architecture.**
McGaughy, Jill A., Newman, Lori, A.

5:00-5:30 **Combined role of primate midcingulate cortex in feedback processing and exploratory decisions.**
Procyk, Emmanuel; Amiez, Cline; Wilson, Charles R.E.; Stoll, Frederic

5:30-6:00 **Comparison of the organisation of the ACC using rs-fMRI in humans and animal models.**
Sallet, Jerome; Lopez-Persem, Alizee; Rushworth, Matthew, Mars, Rogier

6:00-6:30 **Break – Exhibits.** *Camino Hall*

6:30-8:30 **Poster Session 1**. *Camino Hall*

1. **Hippocampal Cav1.2 channels mediate extinction of cocaine-associated memories via dopamine D1R activation.**
   Burgdorf, Caitlin E.; Fischer, Delaney; Bavley, Charlotte C.; Martinez-Rivera, Arlene; Hackett, Jonathan; Rajadhyaksha, Anjali M.
2. **Acute administration of estradiol or progesterone during conditioning leads to divergent effects on the acquisition and expression of cocaine CPP.**
   Kokane, Saurabh; Perrotti, Linda.
3. **Effects of ICI 182,780 on preference for cocaine in male rats.**
   Quigley, Jacqueline; Lalani, Lahin; Lipkin, Benjamin; Becker, Jill
4. **Localizing the role of Homer2 in regulation of methamphetamine reinforcement.**
   Brown, Chelsea; Fultz, Elissa; Ferdousian, Sami; Rogers, Sarina; Lustig, Eli; Kippin, Tod; Szumlinski, Karen
5. **Within animal comparison of neuronal ensembles engaged by novelty and drug reward.**
   Nawarawong, Natalie N.; Slaker, Megan; Olsen, Christopher M.
6. **What is the role of subcutaneous single injection on the behavior of adult male rats exposed to drugs?**
   Slamberova, Romana; Nohejlova, Kateryna; Ochozkova, Anna; Mihalcikova, Lydia
7. **Optogenetic inhibition of methamphetamine-seeking in rats.**
   Cordie, Rebecca; McFadden, Lisa
8. **The role of the serotonin 1B receptor system in the development of methamphetamine-induced sensitization.**
   Moriya, Yuki; Kasahara, Yoshiyuki; Hagino, Yoko; Hall, F. Scott; Hen, Ren; Ikeda, Kazutaka; Uhl, George R.; Sora, Ichiro
9. **A ketogenic diet improves biconditional association task acquisition and decreases anxiety-like behavior in young and aged rats.**
   Truckenbrod, Leah; Hernandez, Abbi; Campos, Keila; Moon, Brianna; Federico, Quinten; Burke, Sara N.
10. **Aging dependent changes across behavioral phenotypes vary with sex and strain in genetically diverse mouse populations .**
    Green, Torrian; Winter, Shawn; Viands, Emily; Little, Gabriella; Anderson, Laura; Harrison, David; Sukoff Rizzo, Stacey
11. **Behavioral characterization of genetically diverse mouse populations: Implications for improving translation from mouse to human.**
    Sukoff Rizzo, Stacey J.; Anderson, Laura C.; McGarr, Tracy; Green, Torrian L.; Winter, Shawn S; Howell, Gareth R.; Onos, Kristen D.
12. **Androgen receptors and Histone Variant H2A.Z interact to regulate fear memory.**
    Ramzan, Firyal; Azam, Amber B.; Tao, Cindy; Narkaj, Klotilda; Stefanelli, Gilda; Monks, D. Ashley; Zovkic, Iva. B.
13. **Neural response to facial threats following buprenorphine administration in healthy young adults.**

Malcolm-Smith, Susan; du Plessis, Lindie; Meintjies, Ernesta; Ipser, Jonathan; Solms, Mark; Thomas, Kevin. G.F.; Stein, Dan J.; van Honk, Jack

14. **Prefrontal function in fear and avoidance: From reaction to action.**
    Diehl, Maria M.; Bravo-Rivera, Christian; Rodriguez-Romaguera, Jose; Pagan-Rivera, Pablo; Burgos-Robles, Anthony; Roman-Ortiz, Ciorana; Iravedra-Garcia, Jorge; Gonzalez-Diaz, Fabiola; Quirk, Gregory J.
15. **Distinguishing between the contributions of depletion of processing resources and increases in opportunity costs to decline in attentional performance.**
    Phillips, Kyra B.; Rysztak, Lauren; Sarter, Martin
16. **Peripheral inflammation induces acute attentional impairments in rats.**
    Yegla, Brittney; Foster, Thomas
17. **Effects of infusions to the medial prefrontal cortex of an orexin-2 receptor antagonist on attention.**
    Blumenthal, Sarah; Tapp, Austin; Maness, Eden; Burk, Josh
18. **Interaction of rapid estrogenic effects and oxytocin in the mediation of recognition memory.**
    Paletta, Pietro; Smit, Joshua; Collins, Andrila; Choleris, Elena
19. **The rapid effects of hippocampally-synthesized estrogens on recognition learning in ovariectomized mice.**
    Martin, Theresa K.; King, Lauren; Klemens, Melissa; Choleris, Elena
20. **Chronic treatment with Bifidobacterium (Longum, Breve, Infantis) modulates gene expression, neuronal function and structure in rat hippocampus.**
    Mostallino, Maria Cristina; Biggio, Francesca; Talani, Giuseppe; Locci, Valentina; Sanna, Enrico; Biggio, Giovanni
21. **Reduction of GSK3 in the ventral hippocampus impairs development of psychostimulant-induced place preference and novel object location memory.**
    Barr, Jeffrey L.; Shi, Xiangdang; Zaykaner, Michael E.; Unterwald, Ellen M.
22. **Differential representation strategies for delay discounting in the hippocampus and medial prefrontal cortex.**
    Masuda, Akira; Sano, Chie; McHugh, Thomas; Fujisawa, Shigeyoshi; Itohara, Shigeyoshi
23. **Corticotropin-Releasing Factor (CRF) modulation of distinct prefrontal cortex (PFC)-dependent cognitive processes.**
    Hupalo, Sofiya; Berridge, Craig
24. **Sex-differences in hippocampal dopamine release in association with social learning in mice.**
    Matta, Richard; Russell, Madison J.; Limebeer, Cheryl L.; Parker, Linda A.; Choleris, Elena
25. **Acetylcholine signaling in the ventral tegmental area regulates motivation to work for a desirable reward in an effort-based decision-making task.**
    Haight, Joshua; Rathi, Durga; Nunes, Eric; Addy, Nii
26. **Calorie restriction and a viral mimic: Not a straightforward relationship.**
    Kent, Stephen; Kivivali, Leah; Chong, Ken; Kirby, Alice
27. **Gonadal hormones mediate changes in adaptive choice and dopamine release in female rats.**
    Yoest, Katie E.; Shashlo, Kelly E.; Cummings, Jennifer A.; Becker, Jill B.
28. **Prenatal alcohol exposure changes neuronal activations in brain regions mediating the interpretation of facial affect.**
    Lindinger, Nadine; Jacobson, Joseph; Warton, Christopher; Malcolm-Smith, Susan; Molteno, Christopher; Dodge, Neil; Robertson, Frances; Meintjes, Ernesta; Jacobson, Sandra
29. **The development of Cntnap2-related deficits in auditory processing: Implications for neurodevelopmental disorders.**
    Scott, Kaela; Schmid, Susanne; Allman, Brian
30. **Automated motor outcomes in genetic mouse models of neurodevelopmental disorders.**
    Pride, Michael; Silverman, Jill

31. **Nucleus accumbens dopamine modulates social avoidance behavior.**
    Mollinedo-Gajate, I.; Larranaga, M.; Sierra, T.; Fernandez, M.; Penagarikano, O.
32. **Adolescent social isolation in mice is associated with altered sleep-wake behavior and elevated DeltaFosB protein expression.**
    Zhang, Gongliang; Noback, Michael; White, Noelle; Byers, Spencer; Carr, Gregory V.
33. **FKBP52 promotes tau aggregation.**
    Criado Marrero, Marangelie; Gebru, Niat; Blackburn, Roy; Smith, Taylor; Vidal, Yamile; Penny, Hannah; Wang, Xinming; Baker, Jeremy; Koren, John; Dickey, Chad A.; Blair, Laura J.
34. **Primary progressive dynamic aphasia: A case report.**
    Chandregowda, Adithya; Duffy, Joseph, Strand, Edythe; Machulda, Mary; Lowe, Val; Whitwell, Jennifer; Josephs, Keith
35. **COMTval158met polymorphism-modulated response to LPS is regulated through dopamine D1 signaling pathway: A first study linking COMTval158met polymorphism and immune mechanisms.**
    Deslauriers, Jessica; Zhou, Xianjin; Risbrough, Victoria
36. **Musical pleasure affects forward gait in patients with Parkinson's disease.**
    Park, K. Shin; Hass, Chris J.; Patel, Bhavana; Janelle, Christopher M.
37. **Relationship between the risk of mental health disorders and life habits: A cohort study.**
    Mashio, Y.; Yoshizaki, T.; Kawaguchi, H.
38. **Relational memory in the scPCP mouse model for schizophrenia.**
    Trigo, Margarida; Silverman, Jill; Neill, Joanna; Gigg, John
39. **Role of neuroinflammation and amyloid in cognitive impairment in a mouse model of Alzheimer's disease.**
    Zhu, Shenghua; Wang, Jun-Feng; Li, Xin-Min
40. **Effects of experimental concussion by closed head injury on conditioned fear in rats.**
    Rivera-Lopez, Melissa; Sierra-Mercado, Demetrio
41. **Let's get physical: The synergistic effects of exercise and environmental enrichment on behavioral and physiological plasticity in Long-Evans rats.**
    Granger, Megan; Perdomo-Trejo, Jose; Scarola, Samantha; Gerecke, Kim; Bardi, Massimo
42. **Locomotor behavior, hindlimb tendon properties, and epigenetic activity in the spinal cord of developing rats.**
    Bozeman, Aimee L.; Kollmeyer, Leah R.; Burgett, Nicholas; Becker, J.J.; Funk, S.K.; Raveling, A.R.; Schiele, Nathan R.; Doherty, Tiffany S.; Roth, Tania L.; Brumley, Michele R.
43. **The modulatory effect of rosmarinic acid in the rhythmic motor patterns of the lumbar spinal cord of neonatal mice.**
    Mendez, Laura; De Jesus, Kevin; Garcia, Andrea; Diaz, Manuel
44. **Protein synthesis is necessary for rapid, estradiol-facilitated social recognition in female mice.**
    Sheppard, Paul; Asling, Hayley; Armstrong, Sabrina; Elad, Vissy; Vellone, Daniella; Choleris, Elena
45. **Investigation of the social neuroscience of human animal interactions.**
    Wilson, Wendy L.; Cox, Kendra; Coles, Cade; Brown, Tyrel; Waldner, Kacy; Gustafson,Shelby
46. **Role of M1 and M2 muscarinic acetylcholine receptors in social learning in female mice.**
    Ervin, Kelsy; Howard, Sarah; Main, Cecil Dana; Choleris, Elena
47. **Prior experience, an orexin 2 receptor agonist, and cEPo promote anxiolytic behaviors.**
    Yaeger, Jazmine D.W.; Staton, Clarissa D.; Sathyanesan, Samuel; Summers, Cliff H.
48. **Stress resilience: A state of mind, a state of gut.**
    Gururajan, Anand; Ventura-Silva, Ana-Paula; Lyte, Joshy; Becker, Thorsten; Van de Wouw, Marcel; Boehme, Marcus; Mercx, Barbara; Wiley, Niamh; Moloney, Gerard; Stanton, Catherine; Dinan, Timothy; Cryan, John
49. **Managing threat-reward conflict: Strategies of conflict-based decision making.**
    Bravo-Rivera, Hector; Rubio-Arzola, Patricia; Rodriguez-Aquino, Paula; Caban-Murillo, Albit; Quirk, Gregory

50. **What the health? Investigating the immunomodulatory effects of stress and environmental enrichment in Long-Evans rats.**
    Scarola, Samantha; Perdomo-Trejo, Jose; Granger, Megan; Gerecke, Kim; Bardi, Massimo
51. **Acute stress response to the "panel-out" TSST protocol among African American and white college students.**
    Parada, Jennifer; Birkett, Melissa
52. **Neural and endocrine correlates of maternal buffering of fear in vulnerable infants.**
    White, Amanda M.; Hider, Joanna; Chang, Da-Jeong; Sullivan, Regina M.; Akil, Huda; Debiec, Jacek

Saturday, June 30

8:00-9:00 **Keynote Speaker: Sex differences in motivation and addiction.**
Becker, Jill B., University of Michigan, Ann Arbor, MI, USA. *Great Hall South*

9:00-9:30 **Refreshment Break – Exhibits.** *Camino Hall*

9:30-11:30 **Past-Presidents Symposium: Granularity mismatch in behavioral neuroscience: Do advances in the control of neuronal circuits produce commensurate gains in our understanding of how normal and abnormal behaviors are expressed?** Chair: John Bruno, The Ohio State University; Co-Chair: Kelly Lambert, University of Richmond. *Granada ABC*

- 9:30-10:00 **In search of relevant biobehavioral umwelts in preclinical neuroscience investigations: Aligning behavioral and neurobiological approaches in animal models of depression and emotional resilience.**
  Lambert, Kelly
- 10:00-10:30 **Understanding the molecular basis of adaptive environmental interaction with the deep genome in the context of behavioral models of stress related mental disorders.**
  Hunter, Richard G.
- 10:30-11:00 **Convergent neural biomarkers to bridge the species divide in behavioral neuroscience for psychiatric research.**
  Young, Jared; Bhakta, Savita; Bismark, Andrew; Light, Gregory; Swerdlow, Neal; Cavannagh, James; Brigman, Jonathan
- 11:00-11:30 **Lessons learned from a behavioral neuroscience approach to the animal modeling of clinical syndromes.**
  Bruno, John P.; Valentini, Valentina; Phenis, David; Schumacher, Jackson

9:30-11:30 **Symposium: Using genetic mouse models to understand the synapse in cognition and disease.** Chair: Elizabeth Manning, University of Pittsburgh. Co-Chair: Jess Nithianantharajah, The Florey Institute of Neuroscience and Mental Health. *Great Hall North*

- 9:30-10:00 **Neural activity and deficits in executive control in GluN2B conditional knockout mice.**
  Marquardt, Kristin; Kenton, Johnny; Brigman, Jonathan
- 10:00-10:30 **Using in vivo calcium imaging to study prefrontal cortex contributions to OCD: Investigating reversal learning in the SAPAP3 knockout mouse model.**
  Manning, Elizabeth E.; Hyde, James; Dombrovski, Alexandre Y.; Torregrossa, Mary M.; Kass, Robert E.; Ahmari, Susanne E.
- 10:30-11:00 **Unravelling the role of neuroligins in decision-making.**
  Nithianantharajah, Jess
- 11:00-11:30 **Touchscreen learning in genetic mouse models of neurodevelopmental disorders.**
  Pride, M.C.; Adhikari, A.; Petkova, S.; Silverman, J.L.

9:30-11:30 **Symposium: What doesn't kill you makes you stronger! Exploring the biobehavioral mechanisms underlying resilience and adaptation to early-**

life adversity. Chair: Susanne Brummelte, Wayne State University. Co-Chair: Amanda Kentner, MCPHS University. *Great Hall South*

9:30-10:00 **Stress resilience: A state of mind, a state of gut.**
Gururajan, Anand; Ventura-Silva, Ana-Paula; Lyte, Joshy; Becker, Thorsten; Van de Wouw, Marcel; Boehme, Marcus; Mercx, Barbara; Wiley, Niamh; Moloney, Gerard; Stanton, Catherine; Dinan, Timothy; Cryan, John

10:00-10:30 **Please stop poking me! Influence of maternal care on the consequences of neonatal pain exposure in male and female rats.**
Brummelte, Susanne

10:30-11:00 **Harnessing the environment to promote resiliency to early life adversity.**
Kentner, Amanda C.

11:00-11:30 **Epigenetic consequences of exposure to developmental adversity.**
Roth, Tania L.

11:30-1:30 **Lunch Break** (lunch is not provided)

11:30-1:30 **Meet the Professionals Speed Mentoring.** Chair: Cindy Barha, University of British Columbia. *Great Hall South*

All trainees are encouraged to sign-up for this traditional IBNS career development event! Each year a diverse range of successful, behavioral neuroscience professionals from institutions across the globe gather at IBNS - Meet the Professionals gives small groups of trainees the opportunity to network with these professional members in a friendly and relaxed setting. For this year's event, we will be trying a 'speed-dating' style, so trainees will speak with at least three professionals! Trainees are asked to sign-up for this event at the Student/Postdoctoral Social, the registration desk, or by emailing the IBNS Council Student Representative, Cindy Barha (or hunting her down at the meeting). Seats are limited, so be sure to sign up early! The Meet the Professional Speed Mentoring event will be held from 11:30-12:30, allowing participants to have lunch on their own before the scientific sessions resume in the afternoon.

1:30-3:30 **Symposium: Neurobiology of cannabinoid type 2 receptors.** Chair: Hiroki Ishiguro, University of Yamanashi. Co-Chair: Emmanuel Onaivi, William Paterson University. *Granada ABC*

1:30-2:00 **Cannabinoid type 2 receptors in dopamine neurons modify anxiety-like behaviors and alcohol and cocaine conditioned place preference.**
Canseco-Alba, Ana; Onaivi, Emmanuel

2:00-2:30 **Environmental stressors induce psychosis based on genetic variation of Cannabinoid CB2 Receptors.**
Hiroki, Ishiguro; Kouichi, Tabata; Chiaki, Mochizuki; Emmanuel, Onaivi

2:30-3:00 **Cannabinoid receptor genetics: From mice to human subjects.**
Onaivi, Emmanuel S.; Canseco-Alba, Ana; Liu, Qing-Rong; Ishiguro, Hiroki

3:00-3:30 **Microglial and dopaminergic-neuron-specific deletion of CB2 cannabinoid receptors in stress induced neuroinflammation and behavior.**
Sanabria, Branden; Canseco-Alba, Ana; Liu, Qing-Rong; Ishiguro, Hiroki; Onaivi, Emmanuel S.

1:30-3:30 **Symposium: Nicotinic cholinergic signaling in neurological and psychiatric disorders: Insights from mouse models.** Chair: Vinay Parikh, Temple University, Philadelphia. Co-Chair: Jared W. Young, University of California at San Diego. *Great Hall South*

1:30-2:00 **Impact of nicotine on aberrant reward processing in a mouse model of HIV.**
Barnes, Samuel A.; Young, Jared W.; Grant, Igor; TMARC

2:00-2:30 **The role of 7 nicotinic acetylcholine receptors (NACHRS) in neuroinflammation-mediated cognitive impairment.**
Cortez, IbDanelo; Hernandez, Caterina; Ishimwe, Egide; Dineley, Kelly

2:30-3:00 **Neurochemical circuit mechanisms underlying cognitive inflexibility in nicotine dependence.**
Parikh, Vinay; Cole, Robert D.; Zimmerman, Matty; Wolsh, Cassandra; Matchanova, Anastasia; Kutlu, Munir G.; Gould, Thomas J.

3:00-3:30 **Chrna5 neurons in models of Alzheimer's disease: Consequences for neurophysiology in prefrontal cortex and beyond.**
Lambe, Evelyn; Proulx, Eliane; Sparks, Daniel; Venkatesan, Sridevi

1:30-3:30 **Symposium: Sensory processing and integration in neurodevelopmental disorders.** Chair: Susanne Schmid, University of Western Ontario. Co-Chair: Kaela Scott, University of Western Ontario. *Great Hall North*

1:30-2:00 **Neurodevelopmental disruption of auditory processing in rats lacking the autism-candidate gene CNTNAP2.**
Allman, Brian; Scott, Kaela; Schmid, Susanne

2:00-2:30 **Cellular and circuit mechanisms of neocortical dysfunction in Autism Spectrum Disorder.**
Frick, Andreas

2:30-3:00 **Multisensory temporal function in autism: Links to communication.**
Wallace, Mark T.

3:00-3:30 **Role of Cntnap2 in the development of social vocalizations in mice.**
Penagarikano, Olga.

3:30-4:00 **Refreshment Break – Exhibits.** *Camino Hall*

4:00-6:00 **Symposium: Disruptions of parental experiences: Neurobiological and behavioral effects in parental responsiveness and offspring development**. Chair: Molly Kent, University of Richmond. *Great Hall North*

4:00-4:30 **Paternally-mediated transgenerational plasticity in stickleback fish.**
Bell, Alison

4:30-5:00 **Multigenerational impact of female opioid exposure on offspring metabolic risk factors.**
Vassoler, Fair M.; Toorie, Anika M.; Byrnes, Elizabeth M.

5:00-5:30 **Sex-dependent neuroendocrine, neuroinflammatory, and behavioral responses to paternal deprivation in the biparental California mouse**

(Peromyscus californicus).
Glasper, Erica, R.; Khantsis, Sabina; Walker, Shakeera, L.; Madison, Farrah, N.

5:30-6:00 **An investigation of restricted environmental resources, threat presence and maternal responsiveness on offspring brain and behavioral development.**
Kent, Molly

4:00-5:45 **Oral Session 2:** Chair: Davide Amato, Medical University of South Carolina. *Great Hall South*

4:00-4:15 **Synergistic effects of maternal immune activation and adolescent cannabinoid exposure on schizophrenia-related behaviour and prediction error responses in rats**
Dunn, Ariel; Harms, Lauren; Mateer, Abbey; Fulham, Ross; Cooper, Gavin; Todd, Juanita; Hodgson, Deborah; Michie, Patricia

4:15-4:30 **The therapeutic potential of cannabidiol (CBD) in a transgenic mouse model of Alzheimer's disease.**
Watt, Georgia; Schumacher, Carolin; Ittner, Arne; Przybyla, Magda; Ittner, Lars; Li, Henry; Brett Garner; Karl, Tim

4:30-4:45 **Microglia program anxiety and stress regulating brain regions early in life.**
Nelson, Lars H.; Warden, Spencer; Lenz, Kathryn M.

4:45-5:00 **Exposure to fluoxetine during adolescence in female C57BL6 mice results in an anxiogenic-like behavioral phenotype in adulthood.**
Iniguez, Sergio; Flores-Ramirez, Francisco

5:00-5:15 **DYRK1A as a prototype of gene involved in neurodevelopmental disorders. Lessons learnt from modeling in the mouse and in the rat.**
Herault, Yann ; Dubos, Aline; Duchon, Arnaud; Nguyen, Thu Lan; Marchal, Damien; Chevalier, Claire; Pani, Guillaume; Muniz Moreno, Maria del Mar; Brault, Vronique

5:15-5:30 **Early SSRI exposure disrupts long-term behavioral responses to social and sensory stimuli.**
Maloney, Susan E.; Akula, Shyam; McCullough, Katherine B.; Chandler, Krystal; Dougherty, Joseph D.

5:30-5:45 **Characterising and exploiting δ subunit-containing $GABA_A$ receptors as novel targets for treating social disorders.**
Bowen, Michael T.; Jones, Kathryn; Chebib, Mary

5:45-6:00 **Sex differences in brain-resident immune cells and the early life programing of social behavior.**
Lenz, Kathryn M.; Vanderhoof, Douglas; Joshi, Aarohi

4:00-5:30 **Symposium: Factors influencing replicability of behavioral neuroscience studies.** Chair: Polymnia Georgiou, University of Maryland School of Medicine. Co-Chair: Todd D. Gould, University of Maryland School of Medicine. *Granada ABC*

4:00-4:30 **Replication of Genome-Wide Association Studies (GWAS) of behavioral and physiological traits in an advanced intercross mouse line.** Palmer, Abraham A.; Zhou, Xinxin; Gonzales, Natalia

4:30-5:00 **Assessing replicability of mouse behavioral genetic studies through aggregated experimental results.**
Chesler, Elissa J.; Philip, Vivek M.; Bogue, Molly A.

5:00-5:30 **Human experimenter sex modulates mouse behavioral responses to stress and to the antidepressant ketamine.**
Georgiou, Polymnia; Zanos, Panos; Jenne, Carleigh; Highland, Jaclyn; Gerhard, Danielle; Duman, Ronald; Gould, Todd D.

6:00-6:30 **Break – Exhibits.** *Camino Hall*

6:30-8:30 **Poster Session 2**. *Camino Hall*

1. **Effect of microglial suppression by pre-treatment of the periadolescent rat with minocycline on nicotine-induced sensitization to cocaine reward in the adult.**
   Svenson, Brooke E.; Nagchowdhuri, Partha S.; Williams, Helen L.; McMillen, Brian A.
2. **Drebrin regulates opiate-induced behavioral and structural plasticity in the Nac.**
   Martin, Jennifer; Werner, Craig; Zhong, Ping; Wang, Zi-Jun; Siemian, Justin; Hagarty, Devin; Neve, Rachael; Li, Jun-Xu; Chandra, Ramesh; Lobo, Mary-Kay; Gancarz, Amy; Yan, Zhen; Dietz, David
3. **Neuroinflammatory modulation of nicotine dependence.**
   Anderson, Erin L., Adeluyi; Adewale; Turner, Jill R.
4. **Is there a cognitive cost to inhibiting cocaine relapse with mGlu5 receptor antagonism?**
   Gobin, Christina; Schwendt, Marek
5. **Cocaine seeking ensembles in the medial prefrontal cortex following early and late abstinence.**
   Slaker, Megan; Nawarawong, Natalie N.; Olsen, Christopher, M.
6. **The effects of chemogenetic inhibition of prelimbic cortical inputs to the paraventricular nucleus of the thalamus on cue- and cocaine-induced drug-seeking behavior in sign-trackers vs. goal-trackers.**
   Kuhn, Brittany; Campus, Paolo; Klumpner, Marin; Flagel, Shelly
7. **Resolving the neural circuitry of Social Familiarity induced Anxiolysis (SoFiA) using Gi-DREADDs.**
   Majumdar, S., Abreu, A., Lungwitz, E.A., Bharadwaj, N., Andrews, K.D., Dietrich, A.D., Truitt, W.A.
8. **A role for the histone lysine demethylase KDM6B in Alcohol Use Disorder (AUD) and neuroinflammation.**
   Vilca, S.J.; Johnstone, A.L.; Andrade, N.S.; Barbier, E.; Khomtchouk, B.B.; Rienas, C.A.; Lowe, K.; VanBooven, D.J.; Tapocik, J.D.; Meinhardt, M.W.; Sartor, G.C.; Zeier, Z.; Sommer, W.H.; Heilig, M.; Wahlestedt, C.
9. **Maternal care effects on anxiety and alcohol consumption.**
   Bui, Ashley; Cameron, Nicole M.
10. **Zebrafish responds to alcohol in the water before it reaches its brain.**
    Tsang, Benjamin; Tran, Steven; Chow, Hayden; Gerlai, Robert
11. **The role of lateral intercalated cell masses of the amygdala in social buffering of conditioned fear responses in male rats.**
    Kiyokawa, Yasushi; Minami, Shota; Takeuchi, Yukari
12. **Light vs. dark or black vs. white? Illumination vs. background shade preference in the light dark task using zebrafish.**
    Facciol, Amanda; Gerlai, Robert
13. **Effects of intranasal orexin-A on MK-801-induced attentional deficits.**
    Maness, Eden B.; Fadel, Jim R.; Burk, Joshua A.

14. **Effect of DREADD-induced inhibition of cholinergic, glutamatergic and all PPTg neurons on sensorimotor gating.**
    Fulcher, Niveen; Azzopardi, Erin; De Oliveira, Cleusa; Schmid, Susanne
15. **A novel task for studying reconsolidation-related memory updating in rats: a role for muscarinic receptors.**
    Wideman, Cassidy; MacGregor, Chelsea; Kupka, Courtney;Mitchnick, Krista; Winters, Boyer
16. **Optogenetic inactivation of basolateral amygdala in young rats recapitulates aged rats' ability to delay gratification in an intertemporal choice task.**
    Hernandez, Caesar M.; Orsini, Caitlin A.; McQuail, Joseph A.; Bruner, Matt M.; Labiste, Chase; Wheeler, Alexa-Rae; Ten Eyck, Tyler W.; Singhal, Sarthak; Burke, Sara N.; Frazier, C. Jason; Setlow, Barry; Bizon, Jennifer L.
17. **If you give a rat a coffee...: Investigating the effects of caffeine on the cognitive and emotional response in Long Evans male rats.**
    Perdomo-Trejo, Jose; Scarola, Samantha; Granger, Megan; Gerecke, Kim; Bardi, Massimo
18. **Individual differences in cholinergic modulation of 22kHz distress vocalizations in rats during fear conditioning and extinction.**
    Kellis, Devin M.; Kaigler, Kris F.; Wilson, Marlene A.
19. **Disrupting Tip60 improves systems consolidation by indirectly acting on H2A.Z.**
    Narkaj, Klotilda; Azam, Amber; Stefanelli, Gilda; Angco, Alexandria; Servado, Karina; Zovkic, Iva
20. **Enhancing effects of acute exposure to cannabis smoke on working memory performance.**
    Blaes, Shelby L.; Orsini, Caitlin A.; Stubbs, Toneisha D.; Ferguson, Shandera N.; Heshmati, Sara C.; Bruner, Mathew M.; Wall, Shannon C.; Febo, Marcelo; Bruijnzeel, Adriaan W.; Bizon, Jennifer L.; Setlow, Barry
21. **Effort-related decision making in humanized COMT mice: effects of Val158Met polymorphisms and dopamine antagonism.**
    Yang, Jen-Hau; Presby, Rose; Cayer, Suzanne; Rotolo, Renee; Fitch, R. Holly; Correa, Merce; Salamone, John
22. **Change in environment leads to a loss in spatial memory and increases in depressive-like symptoms in rats.**
    Sumaya, Isabel C.; Villarreal, Susie; Hussain, Samirah; Musquez, Morgan; Amick, Charity; Rameriz, Nayeli; Hussain, Anjum; Cabanillas, Irene; Luna, Marisol; Greene, Cassandra.
23. **Fluoxetine, but not scopolamine, requires BDNF induction in the medial prefrontal cortex to mediate antidepressant effects.**
    La Grange, Nicole; Ramaker, Marcia; Dulawa, Stephanie
24. **Effects of the serotonin transport inhibitor fluoxetine on effort-related decision making in male and female rats.**
    Rotolo, Renee; Yang, Jen-Hau; Presby, Rose; Correa, Merce; Salamone, John
25. **The role of corticotropin-releasing factor in depressive-like behavior under conditions of uncertainty.**
    Bryce, Courtney A.; Adalbert, Alexandra J.; Claes, Mona M.; Floresco, Stan B.
26. **Effects of chemogenetic inhibition of dopamine transporter- or A2A-expressing neurons on spontaneous activity and motivation to consume a palatable food reward.**
    Wherry, J.; Jentsch, J.D.
27. **Reward motivation in humans and its relationship to dopamine D2/3 receptor availability: A pilot study with dual [11C]-raclopride and [11C]-(+)-PHNO imaging.**
    Caravaggio, Fernando; Fervaha, Gagan; Browne, Caleb; Gerretsen, Philip; Remington, Gary, Graff-Guerrero, Ariel
28. **Glutamatergic mechanisms in the inferior colliculus play a key role in paradoxical kinesia induced by appetitive 50- kHz ultrasonic vocalisations in rats.**
    Tonelli, Luan; Wöhr, Markus; Schwarting, Rainer; Melo-Thomas, Liana

29. **Adolescent oxytocin treatment alters anxiety-like behaviour elicited by early life stress differently depending on sex.**
    Baracz, Sarah; Carey, Harry; Robinson, Katherine; Turner, Anita; Everett, Nick; Cornish, Jennifer
30. **Drd3 signaling in the lateral septum mediates early life stress-induced social dysfunction.**
    Shin, Sora; Pribiag, Horia; Lilascharoen, Varoth; Knowland, Daniel; Wang, Xiao-Yun; Lim, Byung Kook
31. **Role of Cannabinoid CB1 receptors in mediating the long-term effects of adolescent chronic stress on the behavioral impairments following traumatic brain injury in adult rats.**
    de la Tremblaye, Patricia; Wellcome, Jody; Wiley, Kaitlyn; Cheng, Jeffrey; Bondi, Corina; Kline, Anthony
32. **Stress during puberty has differential effects on impulse action and introduction of delays in reward contingencies.**
    Gonzalez-Martinez, Lina Fernanda; Lee, HongJoo Joanne; Delville, Yvon
33. **Tracking the impact of early-life challenges on neurobiological correlates of social and stress responses in female adult rats.**
    Kovalev, Dmitry; Brooks, Milan; Kent, Molly; Lambert, Kelly
34. **Role of HDAC2 in the treatment for schizophrenia and epilepsy.**
    Ibi, Daisuke; de la Fuente Revenga, Mario; Hiramatsu, Masayuki; Gonzalez-Maeso, Javier
35. **Effects of Cacna1c haploinsufficiency on social interaction behavior and 50-kHz ultrasonic vocalizations in rats.**
    Redecker, Tobias M.; Kisko, Theresa; Braun, Moria; Wöhr, Markus; Schwarting, Rainer K. W.
36. **Modeling selection of voluntary physical activity in psychiatric disorders: effects of the SSRI fluoxetine in rodents.**
    Presby, Rose; Ye, Bryanna; Flynn, Molly; Rotolo, Renee A.; Yang, Jen-Hau; Carratala-Ros, Carla; Correa, Merce; Salamone, John D.
37. **Upregulation of mGlu5 in the basal lateral amygdala and mPFC as a molecular feature of resilience to traumatic stress in rats.**
    Shallcross, John; Schwendt, Marek; Knackstedt, Lori
38. **A single injection of losartan improves neurological outcome in male and female rats subjected to ischemic stroke.**
    Martinez-Jimenez, Solianne; Gonzalez-Vega, Maxine; Ferchmin, Pedro; Martins, Antonio
39. **The role of the cannabinoid 2 receptor in modulating microglia activation after a traumatic brain injury.**
    Zamora, Maria F.; Canseco-Alba, Ana; Liu, Qing-Rong; Onaivi, Emmanuel; Bierbower, Sonya M.
40. **Automated motor outcomes in genetic mouse models of neurodevelopmental disorders.**
    Pride, Michael; Silverman, Jill
41. **Identifying the cell type mediating NMDAR receptor hypofunction effects on behaviours relevant to schizophrenia.**
    Jones, Nigel; Sokolenko, Elysia; Hudson, Matt; Nithianantharajah, Jess
42. **Neuroprotective effect of Rutin in experimental paradigms of STZ-induced diabetic neuropathy.**
    Mittal, Ruchika; Kumar, Anil
43. **Sex- and hormone-dependent effects of stress on astrocyte morphology in medial prefrontal cortex: Structural atrophy in males, hypertrophy in females.**
    Bollinger, Justin L.; Wellman, Cara L.
44. **Identifying neuroprotective in vivo targets after a traumatic brain injury.**
    Zamora, Maria F.; Bierbower, Sonya M.
45. **Canca1c haploinsufficiency in juvenile rats produces sex-dependent effects on social play behavior and pro-social 50-kHz ultrasonic communication in both the sender and receiver.**
    Kisko, Theresa M.; Braun, Moria D.; Michels, Susanne; Witt, Stephanie H.; Rietschel, Marcella; Culmsee, Carsten; Schwarting, Rainer K.W; Wöhr, Markus

46. **Altered emission of isolation-induced ultrasonic vocalizations in Cacna1c haploinsufficient rat pups.**
    Kayumova, Rukhshona; Kisko, Theresa M.; Braun, Moria D.; Schwarting, Rainer K.W.; Wöhr, Markus
47. **Phosphorylation of mitogen-activated protein kinase in the rat mPFC and amygdala is associated with individual variation in extinction learning.**
    Russo, A.S.; Parsons, R.G.
48. **Behavioral changes across novelty habituation: Contextual modulation of self-grooming after a stress event.**
    Rojas-Carvajal, Mijail; Villalobos, Katherine; Fornaguera, Jaime; Brenes, Juan C.
49. **The right fit: Finding the ideal volume and exposure time for drug delivery in zebrafish.**
    Frick, Erin; Caramillo, Erika; Khan, Kanza; Echevarria, David
50. **When behavior drives neurobiological explorations: A preliminary investigation of rodent driving responses and accompanying biomarkers of stress adaptation.**
    Fox, N.; Crawford, E.; Knouse, L.; Vavra, D.; Kent, M.; Lambert, K.
51. **Sex-dependent effects of two-hit stress on behavioral flexibility in rodents.**
    Moench, Kelly M.; Wellman, Cara L.
52. **Changes in myelin structure and fear behavior after blast induced mild traumatic brain injury (mtbi).** Taylor, William; Nonaka, Mio; Holmes, Andrew

Sunday, July 1

8:00-9:00 **Keynote Speaker: Pubertal maturation of male social behavior: Multi-tasking by testosterone.**
Sisk, Cheryl, Michigan State University, East Lansing, MI, USA. *Great Hall South*

9:00-9:30 **Refreshment Break – Exhibits.** *Camino Hall*

9:30-11:30 **Symposium: Regulating fear memories.** Chair: Susan Sangha, Purdue University. Co-Chair: Maria Diehl, University of Puerto Rico. *Great Hall South*

9:30-10:00 **Prefrontal function in fear and avoidance: From reaction to action.**
Diehl, Maria M.; Bravo-Rivera, Christian; Rodriguez-Romaguera, Jose; Pagan-Rivera, Pablo; Burgos-Robles, Anthony; Roman-Ortiz, Ciorana; Iravedra-Garcia, Jorge; Gonzalez-Diaz, Fabiola; Quirk, Gregory J.

10:00-10:30 **Chronic ethanol impairs fear extinction retrieval, intensifies fear memory generalization, and reduces Arc expression in the infralimbic cortex.**
Scarlata, Miranda; Lee, Serena; Kandigian, Savannah; Hiller, Abbi; Lawson, Kate; Soler, Ivan; Ng, Alex; Mousley, Alexa; Bezek, Jessica; Dishart, Julian; Mintz, Gabi; Wang, Ziwen; Bergstrom, H.

10:30-11:00 **Identification and manipulation of fear extinction engrams in the hippocampus.**
Drew, Michael R.; Lacagnina, Anthony F.; Denny, Christine A.

11:00-11:30 **Suppressing conditioned fear in the presence of a safety cue.**
Sangha, Susan

9:30-11:30 **Symposium: Convergent mechanisms underlying rapid antidepressant behavioral actions.** Chair: Panos Zanos, University of Maryland, School of Medicine. Co-Chair: Todd D. Gould, University of Maryland, School of Medicine. *Great Hall North*

9:30-9:54 **GLO1 inhibitors alter GABAergic signaling and exhibit fast-onset antidepressant properties.**
McMurray, K.M.J.; Ramaker, M.J.; Barkley-Levenson, A.M.; Sidhu, P.S.; Elkin, P.K.; Reddy, M.K.; Guthrie, M.L.; Cook, J.M.; Rawal, V.H.; Arnold, L.A.; Palmer, A.A.; Dulawa, S.C.

9:54-10:18 **Positive modulation of the NMDA receptor produces rapid and sustained antidepressant effect: Characterization of Rapastinel's novel mechanism of action.**
Banerjee, Pradeep; Li, Yong-Xin; Donello, John; Burgdorf, Jeffery; Stanton, Patric K.; Moskal, Joseph

10:18-10:42 **GABA interneurons mediate the rapid antidepressant-like effects of scopolamine.**
Wohleb, Eric; Wu, Min; Gerhard, Danielle; Taylor, Seth; Picciotto, Marina; Alreja, Meenakshi; Duman, Ronald

10:42-11:06 **Ketamine and hydroxynorketamines: NMDAR inhibition independent mechanisms underlying rapid acting antidepressant efficacy.**
Zanos, Panos; Gould, Todd

11:06-11:30 **Faster and better: The antidepressant actions of negative allosteric modulators of GABA-A receptors.** Thompson, Scott M.

9:30-10:30 **Symposium: Social environmental and genetic factors contributing to increased vulnerability to drug addiction.** Chair: Giovanni Biggio, University of Cagliari, Italy. Co-Chair: Enrico Sanna, University of Cagliari, Italy. *Granada ABC*

9:30-10:00 **Transcriptional consequences of compulsive methamphetamine taking in the presence of punishment.**
Cadet, Jean Lud

10:00-10:30 **Reduced amygdalar endocannabinoid signalling contributes to high stress vulnerability, anxiety and excessive alcohol drinking in genetically selected alcohol preferring.**
Ciccocioppo, Roberto; Roberto, Marisa, Masi, Alessio; Ubaldi, Massimo; Cannella, Nazzareno

11:30-1:30 **Lunch Break** (lunch is not provided)

1:30-3:30 **Symposium: Abnormal cortical asymmetry as a target for neuromodulation in neuropsychiatric disorders.** Chair: Randy Beck, Institute of Functional Neuroscience, Perth, Australia. Co-Chair: Rohit Shankar, University of Exeter Medical School, Exeter, United Kingdom. *Great Hall South*

1:30-2:00 **Historical developmental models and identification of cortical asymmetries.**
Beck, Randy; Laugharne, Jonathan; Laugharne, Richard; Woldman, Wessel; McLean, Brendan; Mastropasqua, Chiara; Jorge, Ricardo; Beck, Michael; Shankar, Rohit

2:00-2:30 **Modulating Cortical Asymmetry: The transdiagnostic reduction of depressive and anxiety symptoms utilising a novel therapeutic approach.**
Beck, Randy; Laugharne, Jonathan; Laugharne, Richard; Woldman, Wessel; McLean, Brendan; Mastropasqua, Chiara; Jorge, Ricardo; Beck, Michael; Shankar, Rohit

2:30-3:00 **Clinical approaches to treatment of Autistic Spectrum Disorders with non-invasive brain stimulation modalities.**
Beck, Randy; Laugharne, Jonathan; Laugharne, Richard; Woldman, Wessel; McLean, Brendan; Mastropasqua, Chiara; Jorge, Ricardo; Beck, Michael; Shankar, Rohit

3:00-3:30 **Clinical approaches to treatment of psychiatric and neurological disorders with non-invasive brain stimulation modalities.**
Beck, Randy; Laugharne, Jonathan; Laugharne, Richard; Woldman, Wessel; McLean, Brendan; Mastropasqua, Chiara; Jorge, Ricardo; Beck, Michael; Shankar, Rohit

1:30-3:30 **Symposium: Associative brain mechanisms underlying adaptive and maladaptive behavior.** Chair: Donna Calu, University of Maryland School of Medicine. *Great Hall North*

1:30-2:00 **Managing threat-reward conflict: Strategies of conflict-based decision making.**

Bravo-Rivera, Hector; Rubio-Arzola, Patricia; Rodriguez-Aquino, Paula; Caban-Murillo, Albit; Quirk, Gregory

2:00-2:30 **Amygdalar mechanisms driving individual differences in Pavlovian approach and flexibility.**
Nasser, Helen M.; Chen, Yu-Wei; Fiscella, Kimberly; Calu, Donna J.

2:30-3:00 **Modulating aversive prediction error in the dopamine circuit.**
Iordanova, Mihaela D.; Mahmud, Ashraf; Cossette, Marie-Pierre; Esber, Guillem

3:00-3:30 **Encoding of outcome information in the infralimbic cortex during habits and goal-directed actions.**
Barker, Jacqueline M.; Glen, W. Bailey; Linsenbardt, David N.; Lapish, Christopher C.; Chandler, L. Judson

1:30-3:30 **Symposium: Invertebrate models of natural and drug-sensitive reward.** Chair: Moira van Staaden, Bowling Green State University. Co-Chair: Robert Huber, Bowling Green State University. *Granada ABC*

1:30-2:00 **Intoxicated crayfish, addicted flies, and relapsing bees: The conserved nature of drug-sensitive reward.**
Huber, Robert; van Staaden, Moira

2:00-2:30 **Embryonal exposure to amphetamine alters behavior and dopaminergic activity in *C. elegans* adults and progeny.** Ambigapathy, Ganesh; Kudumala, Sirisha R.; McCowan, Talus J.; Dhasarathy, Archana; Carvelli, Lucia.

2:30-3:00 **The effects of alcohol on crayfish neural circuitry and behavior depend on prior social experiences.**
Herberholz, Jens

3:00-3:30 **The effect of mammalian drugs of abuse on the drug sensitive circuitry in Crayfish.**
Orfanakos, Vasiliki B.; Shipley, Adam T.; Wormack, Leah N.; Nathaniel, Thomas I.; Imeh-Nathaniel, Adebobola; Huber, Robert

3:30-4:00 **Refreshment Break – Exhibits.** *Camino Hall*

4:00-6:00 **Symposium: Using schedules of partial reinforcement to test uncertainty effects in a learning diathesis model of anxiety vulnerability.** Chair: Todd Allen, University of Northern Colorado. Co-Chair: Justin Handy, Syracuse VA Medical Center. *Granada ABC*

4:00-4:30 **Eyeblink conditioning is enhanced in behaviorally inhibited individuals in uncertain training protocols.**
Allen, Todd

4:30-5:00 **Enhanced acquisition and one-week retention of the classically conditioned eyeblink response in veterans self-reporting post-traumatic stress disorder symptoms.**
Handy, Justin; Servatius, Richard

5:00-5:30 **Partially reinforced avoidance learning reveals differences in the expectation versus the presence of shock in Wistar-Kyoto rats.**
Miller, Daniel P.; Servatius, Richard J.

5:30-6:00 **Applications of the learning diathesis model of anxiety disorders.**
Servatius, Richard

4:00-5:30 **Oral Session 3:** Chair: Kim Gerecke, Randolph-Macon College. *Great Hall North*

4:00-4:15 **Clozapine blunts nicotine self-administration and reinstatement of nicotine-seeking, but increases motivation for food.**
Abela, Andrew R.; Li, Zhaoxia; L.; Anh, D.; Fletcher, Paul J.

4:15-4:30 **Differential encoding of sensitization and cross sensitization to psychostimulants and antipsychotics in nucleus accumbens D1- and D2-receptor expressing medium spiny neurons.**
Amato, Davide; Heinsbroek, Jasper; Kalivas, Peter W.

4:30-4:45 **High ambient temperatures increase the lethality of methylenedioxymethamphetamine and methcathinone.**
Chen, Yu; Tran, Huyen T.; Hefflinger, Courtney J.; Muskiewicz, Dawn E.; Hall, F. Scott

4:45-5:00 **Influences of experimental conditions and stress on the escalation of ethanol consumption in male and female mice.**
Muskiewicz, Dawn E.; Frommann, Nicole P.; Patel, Bijal R.; Simon, Audrey C.; Lin, Zhicheng; Hall, F. Scott

5:00-5:15 **Ethanol affects neutral sphingomyelinase-induced changes in depression/anxiety state of mice.**
~~Kalinichenko, Liubov S.~~ CANCELED; Lacatusu, Laura; Ulrich, Franziska; Gulbins, Erich; Kornhuber, Johannes; Mueller, Christian P.

4:00-5:30 **Oral Session 4:** Chair: Farida Sohrabji, Texas A&M Health Science Center. *Great Hall South*

4:00-4:15 **Stromalin constrains memory acquisition by developmentally limiting synaptic vesicle pool size.**
Phan, Anna; Thomas, Connon I.; Chakraborty, Molee; Berry, Jacob A.; Kamasawa, Naomi; Davis, Ronald L.

4:15-4:30 **Study on multi-Drosophila social behavior monitoring in high-dynamic-range environment by computer vision.**
Ching Hsin Chen, Po Yen Hsiao, Yi Ting Chen, Ann Shyn Chiang, Hung Yin Tsai

4:30-4:45 **Genetic, developmental and neural correlates of excessive grooming in an invertebrate model of neurofibromatosis type 1.**
King, Lanikea B.; Tomchik, Seth M.

4:45-5:00 **Behavioral and neuroimmunological consequences of maternal allergic asthma.**
Schwartzer, Jared; Church, Jamie

5:00-5:15 **A high-sucrose maternal diet has enduring effects on offspring brain and behavior in rats: a possible role for neurosteroids.**
Tobiansky, Daniel J.; Kachkovski, George; Schmidt, Kim L.; Enos, Reilly T.; Ma,

	Chunqi; Tomm, Ryan J.; Hamden, Jordan E.; Jalabert, Cecilia; Floresco, Stan B.; Murphy, E. Angela; Soma, Kiran K.
6:00-7:00	**IBNS Business Meeting** (Open to all members). *Granada ABC*
8:00-midnight	**IBNS Awards Banquet.** Theme: Miami Vice. *Great Hall North & South.*

ABSTRACTS

Thursday, June 28

8:00-9:00 **Presidential Lecture: Avoiding danger at all costs.**
Quirk, Gregory J., University of Puerto Rico School of Medicine, Puerto Rico, USA.

Avoiding danger at all costs. Gregory J. Quirk, Depts. of Psychiatry and Anatomy & Neurobiology, Univ. of Puerto Rico School of Medicine, San Juan, PR. We are nearing three decades of research on the neural circuits of Pavlovian fear conditioning. The advent of transgenic and optogenetic techniques have greatly advanced our understanding of fear conditioning circuits and their potential applicability to anxiety disorders such as PTSD and OCD. Under natural conditions, however, animals (and humans) make decisions to avoid potential threats, and these decisions compete with appetitive drives. Research on active avoidance is experiencing a resurgence with naturalistic tasks in rodents, monkeys and humans that incorporate decision making into fear learning models. A prefrontal-amygdala-striatal network is emerging that assesses both threats and rewards to maximize active behavioral responses.

9:30-11:30 **Symposium: Social neuroscience in rodents: Neural foundations and clinical implications.** Chair: Markus Wöhr, Philipps University of Marburg. Co-Chair: Jill L. Silverman, University of California Davis.

Rodent Ultrasonic Communication: Brain and Behavior. Markus Wöhr; Behavioral Neuroscience, Experimental and Biological Psychology, Faculty of Psychology, Philipps-University of Marburg, Gutenbergstr. 18, D-35032 Marburg, Germany. Mice and rats are highly social animals, with a rich social behavior repertoire, including the emission of ultrasonic vocalizations (USV). In rats, typically three main types of USV are distinguished: (I) Isolation-induced 40-kHz USV in pups, as well as (II) aversive 22-kHz USV and (III) appetitive 50-kHz USV in juvenile and adult rats. Specifically, 22-kHz USV occur in aversive situations, such as predator exposure and fighting, while 50-kHz USV occur in appetitive situations, such as social play and mating, or in response to psychostimulants, e.g. amphetamine. Evidence from selective breeding, devocalization, and playback studies suggests that 22-kHz and 50-kHz USV serve as situation-dependent socio-affective signals with distinct communicative functions, e.g. 50-kHz USV as social contact calls. While 22-kHz USV fulfill an alarming function and induce freezing in the receiver, 50-kHz USV evoke a social approach response. The opposite behavioral responses are paralleled by distinct brain activation patterns. Freezing elicited by alarming 22-kHz USV is accompanied by increased neuronal activity in brain areas regulating fear and anxiety, e.g. amygdala. In contrast, social approach evoked by pro-social 50-kHz USV is paralleled by reduced amygdala activity, but enhanced activity levels and dopamine release in the nucleus accumbens, a brain area implicated in reward processing. In a recent series of studies, we assessed the validity of 50-kHz USV as a marker for mania-like elevated mood and hypersociability. We showed that amphetamine treatment leads to enhanced 50-kHz USV emission and increased social approach behavior in response to 50-kHz USV playback. Importantly, the amphetamine-induced increase in 50-kHz USV can be blocked by the 5-HT2c receptor agonist CP 809,101 as well as lithium, the gold standard for treating bipolar disorder in humans. Moreover, we showed that a novel genetic rat model for Cacna1c haploinsufficiency displays deficits in pro-social 50-kHz USV. Specifically, 50-kHz USV levels emitted by the sender during social play as well as social approach behavior elicited by 50-kHz USV playback in the receiver were found to be reduced in Cacna1c haploinsufficient rats. CACNA1C is a cross-disorder risk gene strongly implicated in multiple neuropsychiatric disorders, including autism spectrum disorder and bipolar disorder. Together, 50-kHz USV might therefore serve as a novel marker for deficits in socio-affective functioning with relevance for neuropsychiatric disorders.

Developmental Social Communication in Two Genetic Rat Models of Neurodevelopmental Disorders Elizabeth L. Berg, Markus Wöhr and Jill L. Silverman. MIND Institute and Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, CA 95817. Phelan McDermid Syndrome (PMS) and Angelman Syndrome (AS) are rare neurodevelopmental disorders characterized by developmental delay, impaired

receptive and expressive social communication skills, motor and balance deficits, poor attention, intellectual disabilities, and seizures. Mutations in the *SHANK3* gene (SH3 and multiple ankyrin repeat domains 3) lead to PMS. The genetic cause of AS is loss of expression in the brain of *UBE3A* (ubiquitin-protein ligase E6-AP). Forefront strategies have generated preclinical model organisms with a high degree of genetic conservation relative to humans for targeted therapeutic development with gene mutations in Ube3a and Shank3, respectively, (i.e., rats). We utilized these genetic rat tools to quantify outcomes for social communication, and other symptoms across neurodevelopmental disorders. Genetic rat models provide us the opportunity to investigate complex behaviors that have been difficult to capture with signal sensitivity in mice, such as developmental, and juvenile acoustic social communication. We will illustrate new data that tested the effect(s) of *Ube3a* and *Shank3* deletions on behavioral responses to acoustic communication in pups and juvenile rats. We found subtle social communication deficits in both the *Ube3a* and *Shank3* rat models in pup ultrasonic vocalizations and by presenting individual rats with a natural 50-kHz USV versus an acoustic control stimulus, and comparing subsequent USV production and approach behavior toward the stimulus source. We conclude that rats have better signal detection for subtle sophisticated behavior, such as sophisticated social communication. We further conclude that the richer repertoire and sophisticated developmental interactions adds elements of complexity over mouse models that will need to be further investigated. The data presented here lend support for the use of transgenic rat models as tools to study the neurobiology underlying the behavioral phenotypes in neurodevelopmental disorders.

Time-scales of auditory cortical neurons for coding and classifying timing cues found in non-speech vocalizations. Read[1,2], H.L., and Escabi[1,2,3], M.A. [1]Department of Psychological Sciences, [2]Department of Biomedical Engineering, [3]Department of Electrical Engineering. University of Connecticut. Though auditory cortex is essential for perception of timing cues in sound, it remains an open question how cortical neurons integrate temporal cues in the sound envelope in order to recognize and classify vocal communications. Here we examine the statistics of timing cues in the sound envelope for vocalizations sequences from several species including birds, rats and humans. Interestingly, we find the acoustical edges and vocalization durations are major determinants of the $1/f^2$ modulation frequency (Fm) statistics; whereas, the fine temporal fluctuations in the sound envelope are not. Furthermore, vocalization duration sets the upper limit on the vocalization rate and hence could be used to classify different vocalizations. Using a set of "synthetic vocalizations" with sound bursts that co-vary in onset slope and duration much like natural vocalizations, we address explore possible neural codes for classifying vocalizations in three auditory cortical fields. We find a progressive increase in the time scale for neural integration and classification of timing cues in sound burst sequences as one moves from primary to secondary auditory cortical fields. This supports a framework where spike-timing patterns from primary and secondary cortices provide complementary temporal codes that could be used to classify vocalizations. Acknowledgements. NSF 1344065 (Read, PI, Escabi, Co-PI) and NIH, DC014138 (Escabi PI, Read, Co-I).

Social Decision Making in Rats. Marijn van Wingerden[1], Mireille van Berkel[1], Sander van Gurp[1], Mohammad Seidisarouei[1] [1]Social Rodent Lab, University of Düsseldorf, Germany. Rats are highly social animals living in large groups characterized by hierarchies, with a rich and complex social behavior repertoire. In the lab, rats have been shown to act pro-socially and perform helping behavior. These results seem to suggest that rats place a value on the well-being of, or outcomes delivered to their peers. If so, this process of social valuation should be observable in tasks sensitive to value estimation and manipulation. We aimed to quantify these social preferences with a range of behavioral paradigms. Adapting the 3-chambered social maze, we examined and quantified rats' social preferences when choosing to spend time investigating a conspecific or a non-social outcome, equating one in terms of the other. Using reinforcement learning paradigms, we examined whether social value can unblock learning about cues that predict reward delivery to others. We have found that, indeed, rats act as if trading off social reward and non-social reward based on their relative appetitive strength. Furthermore, we have found that social outcomes can unblock reinforcement learning, suggesting that rats process social value as valuable to themselves. Rats in these paradigms emit ultrasonic vocalisations (USVs), a prime candidate signal for transmitting social value. Playback of USVs results in Dopamine (DA) release, making the dopamine-producing cells in the VTA, that are involved in socially motivated (reward) seeking behavior in turn a candidate for representing such value

signal. Using single-cell electrophysiology, we recorded activity from VTA-DA producing cells during playback of USV and indeed found a subset of cells responding differentially to the valence of the USV playback.

Glutamatergic mechanisms in the inferior colliculus play a key role in paradoxical kinesia induced by appetitive 50-kHz ultrasonic vocalisations in rats. Luan Castro Tonelli[1], Markus Wöhr[1], Rainer K. W. Schwarting[1], Liana Melo-Thomas[1]. [1] Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, Gutenbergstrasse 18, 35032 Marburg, Germany. Immobile parkinsonian patients may be able to make quick movements, when excited by external stimuli. This is a phenomenon called paradoxical kinesia (PK) which refers to a sudden transient ability of akinetic patients to perform motor tasks they are otherwise unable to perform. The mechanisms underlying this phenomenon are unknown. However, in a previous study we proposed a new animal model to investigate PK in akinetic rats using species-relevant signals, namely rat ultrasonic vocalizations (USV) which are typical for social situations with positive valence like juvenile play or sexual encounters. Our aim in the present study was to uncover underlying brain mechanisms of PK. We focused on the inferior colliculus (IC) since it not only serves as an acoustic relay station, but can also modulate haloperidol-induced catalepsy. To test the role of the IC in PK induced by 50-kHz USV, male rats received intracollicular administration of NMDA (30nmol) or diazepam (10µg or 20µg) or its respective controls 10 min before haloperidol (0.5 mg/kg; ip). Rats were exposed to playback of 50-kHz USV, white noise, background noise or silence, 10 min each with 5 min intervals. The catalepsy test was measured during the bar test, which consists of placing the rat with its forepaws on a horizontal bar. The time until it stepped down was measured (maximum 600s). In animals which had received saline or vehicle microinjections into the IC, playback of 50-kHz USV significantly reduced haloperidol-induced catalepsy, and no such effects were observed in the case of other stimuli. However, the intracollicular administration of NMDA prevented the playback of 50-kHz USV effect on haloperidol–induced catalepsy. In contrast, although intracollicular diazepam microinjection potentiated the haloperidol-induced catalepsy, it did not affect the response to 50-kHz USV. Therefore, although both drugs microinjected into the IC potentiated haloperidol-induced catalepsy, they differ in their response to the 50-kHz USV playback. The agonist (NMDA) suppressed the effectiveness of the 50-kHz playback whereas the microinjection of the agonist GABA (diazepam) did not prevent the PK induced by the 50-kHz playback. These findings suggest that the neurobiological mechanisms underlying PK through the IC may be rather glutamatergic than GABAergic. Our approach to studying PK might be useful for uncovering the mechanisms behind this phenomenon and improving behavioural therapies for Parkinson's disease. We thank the Deutsche Forschungsgemeinschaft (DFG; ME4197/2-1) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; BEX 13557/13-0).

9:30-11:30 **Symposium: Optimizing brain performance: Identifying mechanisms of adaptive neurobiological plasticity.** Chair: Kelly Lambert, University of Richmond.

Maximizing Neurobiological Affordances via Fine-Tuned Response-Outcome Contingencies. Lambert, Kelly. University of Richmond, Richmond VA 23173. An animal's experiential history and predisposed coping strategies influence the recognition of environmental affordances, viewed as stimuli that predict the possibility of desired outcomes. Extending the notion of environmental affordances to *neurobiological affordances*, our laboratory is interested in identifying response strategies that maximize adaptive neuroplasticity while minimizing allostatic load. Rats exposed to contingency training, for example, exhibit behavioral and neurobiological markers of emotional resilience, including altered markers of neuroplasticity and healthier stress hormone (i.e., corticosterone, DHEA) profiles; additionally, rats profiled as flexible copers exhibit increased markers of neuroplasticity and emotional resilience (i.e., doublecortin- and NPY-immunoreactivity). Further, exposure to natural-enriched environmental conditions alters behavioral responses in a manner that is consistent with emotional resilience ---leading to optimal brain-behavior-environment interactions. In sum, these rodent models provide an opportunity to explore the impact of both predisposed and acquired response strategies on adaptive responses in various challenging contexts, enhancing both environmental and neurobiological affordances throughout an animal's life. This work was supported by NIMH award 1R15H101698-01A1.

Is More Always Better? Optimizing performance with hippocampal neuroplasticity in males and females. Liisa A.M. Galea Ph.D., Shunya Yagi. Djavad Mowafaghian Centre for Brain Health, Graduate Program in Neuroscience, University of British Columbia, 2215 Wesbrook Mall, Vancouver, BC, CANADA, V6T1Z3. There is a long-held assumption that to optimize performance, more new neurons are optimal. However, while this pattern is often seen in males, the pattern can be opposite in females. There are sex differences in severity of cognitive disruptions following stress, and neurodegenerative and psychiatric diseases, many of which are also associated with changes in hippocampal plasticity. For example, chronic restraint stress impairs radial arm maze learning in males but facilitates it in females, and results in differential dendritic pruning in the hippocampus. The hippocampus produces new neurons throughout the lifespan in rodents and humans and adult neurogenesis plays a crucial role for pattern separation and stress regulation in males. However, it is important to establish how neurogenesis in the hippocampus may be involved in hippocampus-dependent cognition in both males and females given the sex differences in cognitive disruptions following diseases that impact the hippocampus. Work in my laboratory indicates that sex differences, favoring males, in spatial navigation and pattern separation. We found that male spatial strategy users outperformed female spatial strategy users only when separating similar, but not distinct, patterns and typically males travel shorter distances to reach a hidden platform than females. Furthermore, male spatial strategy users had greater neurogenesis in response to pattern separation training than all other groups consistent with findings in the Morris Water Maze showing that spatial training increased neurogenesis in males but not in females. Despite this, neurogenesis was positively correlated with performance in females but not in males in both cognitive tasks. These results suggest that the survival of new neurons may play an important positive role for pattern separation of similar patterns in females, despite the fact that more new neurons are not created under learning conditions. Possible factors influencing these sex differences will be discussed. These findings emphasize the importance of studying biological sex on hippocampal function and neural plasticity and have implications for neurodegenerative and psychiatric disorders that target the hippocampus and affect cognition differentially in women versus men. This study was funded by an NSERC grant to LAMG 203596-18.

Crossing the memory-mood divide: Stimulation of entorhinal cortex-dentate gyrus circuitry is antidepressive and improves memory in mice. Amelia J. Eisch[1,2,3] and Sanghee Yun[1,2]. [1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. [2]Children's Hospital of Philadelphia, Philadelphia, PA, USA. [3]Psychiatry Dept, UT Southwestern Medical Center, Dallas, TX, USA. A common perspective on brain – and particularly hippocampal – function emphasizes learning and memory improvements as reflective of improved brain performance. However, the hippocampus subserves a range of brain functions, including memory and mood regulation. These functions have sub-hippocampal regional specificity, as the septal region of the rodent hippocampus (temporal/posterior human hippocampus) is linked to memory, and the temporal region of the rodent hippocampus (septal/anterior human hippocampus) is linked to mood regulation, with some overlap. These subregional functional differences have led to a relative segregation of the research on hippocampal function; for example, it is a rare study that addresses how manipulations influence both memory and mood in either in baseline conditions or in the context of pathology. Here we discuss work on considering this memory-mood divide in Major Depressive Disorder (MDD) and animal models of MDD. As a disorder marked by hippocampal dysfunction - including memory deficits and dysregulated mood - it is notable that MDD is measured by improved depressive-like symptoms often without consideration of whether other hippocampal functions - such as memory - are improved after treatment. Given the current framework for MDD as a "circuitopathy", we discuss our recent preclinical work where brain circuit-specific stimulation improves indices of memory and mood. Specifically we will discuss how stimulation of upstream hippocampal circuitry, the entorhinal cortex, via molecular (knockdown of a psychosocial stress-induced protein) or chemogenetic approaches is both antidepressive and improves hippocampal-dependent memory in mice. These findings emphasize the power and potential of entorhinal cortex afferent stimulation - previously well known for the ability to influence learning and memory in both rodents and humans - for MDD treatment. Funding: NIH, NASA.

Growing Your Neurological (Cognitive) Reserve. Michael Merzenich, University of California San Francisco, Posit Science. Recent studies conducted in animal and human models have now revealed the probable neurological basis of "cognitive

reserve". They have also elucidated natural strategies for amplifying learning rates and elevating asymptotic achievements, especially relevant for struggling human populations. These studies shall be reviewed in the context of strategies for managing brain health in normal and struggling older-adult populations.

9:30-11:00 **Symposium: Neural circuit mechanisms of mouse behavior.** Chair: Yi Zuo, University of California, Santa Cruz. Co-Chair: Ju Lu, University of California, Santa Cruz.

Stress induces synaptic and circuit reorganization in the mouse cerebral cortex. Chia-Chien Chen[1], Ju Lu[1], Renzhi Yang[2], Jun B. Ding[2] and Yi Zuo[1 1]Department of Molecular, Cell and Developmental Biology, University of California, Santa Cruz, CA 95064, USA [2]Department of Neurosurgery, Stanford University School of Medicine, Palo Alto, CA 94304, USA. It is widely accepted that significant experiences can rapidly cause long-lasting alterations of anatomical, physiological, and behavioral properties in the brain. Traumatically stressful experiences can have a profound and enduring influence on emotional and cognitive brain functioning, acting primarily through the dysregulation of synapses, which are the communication sites between neurons. Much is known about the deleterious effects of stress on the affective systems mediated through subcortical structures, but much less has been explored in cortical regions, which are the seats for sensation, perception, learning, memory, cognition, and consciousness. Combining behavioral analyses with *in vivo* synaptic imaging, we show that stressful experiences lead to progressive, clustered loss of dendritic spines along the apical dendrites of layer (L) 5 pyramidal neurons (PNs) in the mouse barrel cortex, and such spine loss closely associates with deteriorated performance in a whisker-dependent texture discrimination task. Furthermore, the activity of parvalbumin-expressing inhibitory interneurons (PV+ INs) decreases in the stressed mouse due to reduced excitability of these neurons. Importantly, both behavioral defects and structural changes of L5 PNs are prevented by selective pharmacogenetic activation of PV+ INs in the barrel cortex during stress. Our findings suggest that the PV+ inhibitory circuit is crucial for normal synaptic dynamics in the mouse barrel cortex and sensory function. Pharmacological, pharmacogenetic, and environmental approaches to prevent stress-induced maladaptive behaviors and synaptic malfunctions converge on the regulation of PV+ IN activity, pointing to a potential therapeutic target for stress-related disorders.

Noradrenergic modulation of sensory processing in the mouse tactile system. Hongdian Yang[1,2], Bilal A. Bari[1], Jeremiah Y. Cohen[1] and Daniel H. O'Connor[1 1] Department of Neuroscience, Johns Hopkins School of Medicine, [2] Department of Molecular, Cell and Systems Biology, University of California, Riverside. The same sensory stimuli can be perceived or neglected, depending on our attention or brain states. What is the underlying neural process that influences our awareness of the presence or absence of the same stimulus? We trained mice to perform a Go/NoGo tactile detection task and made intracellular (whole-cell) recordings in areas of the primary somatosensory cortex (S1) receiving sensory input mainly from the deflected whisker. Under identical whisker deflections, we and others previously found that sensory-evoked membrane potential from the majority of S1 neurons depolarized more prominently when mice successfully detected the tactile stimulus (Hit) compared with when they failed to respond (Miss). What is the underlying neural mechanisms that contribute to the trial-by-trial fluctuations in sensory response and decision making? The locus coeruleus-norepinephrine (LC-NE) system has long been thought to have a critical role in regulating multiple aspects of cognitive behavior, including perception, attentiveness and decision making. To understand how this neuromodulatory system is involved in regulating S1 sensory responses and tactile perception, we made simultaneous extracellular recordings from LC-NE neurons and recordings from S1 neurons during the detection task. We found that LC spiking activity correlated with membrane potential depolarization of S1 neurons as well as behavioral outcomes. Our results suggest that LC-NE inputs modulate sensory information processing to facilitate sensory perception.

Functional diversity of new spines formed during a forelimb-specific reaching task. Lu, Ju[1]; Ma, Shaorong[1]; Zuo, Yi[1]. [1]University of California, Santa Cruz. The ability to manipulate objects dexterously is vital for many mammals. The dexterity develops through practice, and persists once perfected. The underlying mechanism is believed to be the

reconfiguration of neuronal networks in the motor system. Our previous in vivo imaging studies show that motor skill learning induces rapid formation of dendritic spines on layer (L) 5 pyramidal neurons in the motor cortex. Preferentially stabilized by subsequent training, these spines survive beyond the training period, thus providing a structural basis for motor memory. Currently, we are investigating the functional properties of such new spines formed during motor learning. We adapted the single-pellet reaching task for head-fixed mice. We found that mice habituated to head-fixation gradually improved their performance of the task, with the success rate plateauing within 4-8 days of training. They developed a consistent reach trajectory and well-controlled digital movements. Labeling L5 pyramidal neurons sparsely with the genetically-encoded calcium indicator GCaMP6s, we observed Ca transients at the level of individual spines. We found that spine Ca transients were sparse even during animal movement. Based on correlative *in vivo* structural imaging, we successfully identified many new spines formed during training. We found that Ca transients at newly-formed spines had distinct characteristics from those at neighboring stable spines. Newly-formed spines were either persistent or transient, and such fates directly correlated with the properties of Ca transients. Interestingly, not all new spines formed during the training period exhibited coincident activities with successful reaches. We are continuing to investigate the rules that govern new spines' activity patterns and their fate.

1:30-3:30 **Symposium: Environment and the epigenome: How experience contributes to psychiatric illness.** Chair: Zackary A. Cope, University of California, San Diego. Co-Chair: Jared W. Young, University of California, San Diego.

How are maternal-derived signals converted into enduring epigenetic processes in the developing brain? Baram, TZ[1,2], Short AK[1], Bolton JL[1] Depts. [1]Anatomy/Neurobiology, Pediatrics, and [2]Neurology; University of California-Irvine. Mental and cognitive health as well as vulnerability to neuropsychiatric disorders involves an interplay of genes and environment, especially during sensitive developmental periods. Indeed, both genetic and environmental factors contribute to the development and maturation of neurons, synapses and the resulting brain circuits. Whereas the environmental signals for the sculpting of visual and auditory circuits are known (light, sound), the nature of the signals that influence normal or aberrant maturation of emotional and cognitive brain circuits has not been fully resolved. Early in postnatal life, crucial environmental signals arise from the principal care-taker, typically the mother. Thus, in rodent models, the crucial effects of the quantity and qualitative measures of maternal care are well established. However, which maternal signals are salient to optimal brain development, how these signals reach specific populations of neurons and how they influence neuronal and behavioral phenotype enduringly is unclear. We will discuss novel findings suggesting that patterns of maternal behaviors, and specifically fragmented and unpredictable patterns, are a critical factor that influences neuronal circuit maturation and behavioral phenotype. We will demonstrate that maternal signals influence the number and function of synapses abutting specific neuronal populations, which, in turn, is sufficient to initiate epigenetic programs within these neurons. The resulting enduring changes in gene expression translate into altered neuronal function as well as connectivity within brain circuits, and to altered cognitive and emotional behaviors. Finally, we provide evidence across humans and rodents to highlight the importance of predictable sequences of maternal care to optimal cognitive and emotional offspring development. Supported by NS28912; MH73136 and P50 MH096889

Winter-like photoperiods induce psychiatry-relevant behaviors in mice: Evidence for resiliency in mice with reduced dopamine transporter expression. Zackary A. Cope[1], Molly Kwiatkowski[1], Chuck van de Chappelle[2], Maria L. Lavadia[1], Davide Dulcis[1], Jared W. Young[1,3] 1. Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804 2. Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands 3. Research Service, VA San Diego Healthcare System, San Diego, CA. Winter gestation and reduced functional dopamine transporter (DAT) have both been linked to elevated incidences of psychiatric conditions (Cope et al., 2016; Castrogiovanni et al., 1998; Anand et al., 2011). DAT hypomorphic mice with only one functional DAT allele (DAT-HT) exhibit exaggerated depression- and mania-relevant behaviors compared to wildtypes (WT) when exposed as adults to winter- and summer-like photoperiod conditions, respectively (Young et al., in press).

Potential gestational effects of winter-like photoperiod on psychiatry-relevant behaviors have yet to be examined. We hypothesized that winter-like photoperiod would induce psychiatry-relevant behavior in WT mice, which would be exaggerated in DAT-HT mice. Thirtyfour female DAT-WT dams mated, gestated, and reared resulting offspring in either a shortactive (SA, 5 hours dark : 19 hours light) or normal (NA) photoperiods until P28, at which time pups were weaned into tetrads and moved to a standard vivarium room under normal photoperiod. Of this cohort, 75 adult male and female mice were trained to perform nose-poke responses in a five-choice operant chamber (Young et al. 2013). They were then tested on progressive ratio breakpoint (PRB), probabilistic reward learning (PLT), and probabilistic reversal learning (PRL) tasks. In PRB, a significant interaction was observed ($F_{(1,66)}$=4.4, $p<0.05$) as breakpoint was decreased in WT mice reared in SA photoperiod (WT-SA). In the PLT, significant interactions were observed with WT-SA mice exhibiting slowed mean target ($F_{(1,66)}$=7.2, $p<0.01$) and nontarget ($F_{(1,66)}$=4.0, $p<0.05$) response latencies. WT-SA mice also exhibited strong trends to reduced responsiveness such as decreased rewards achieved ($F_{(1,66)}$=3.9, p=0.052), and decreased premature responses ($F_{(1,66)}$=3.9, p=0.051). In the PRL, WT-SA mice produced a strong trend to decreased switches completed ($F_{(1,66)}$=3.712, p=0.058) vs. WT-SA mice. These effects were not observed in DAT-HY mice. Winter-like photoperiod births induce psychiatry-relevant behaviors, reducing effortful motivation and impairing learning, which is also observed in depression and schizophrenia. Interestingly, these results were only observed in the WT mice, not DAT-HT mice. These results suggest that reduced DAT during gestation may convey resiliency to perinatal SA photoperiod. Current efforts are aimed at reproducing these effects as well as investigating possible transgenerational inheritance in an F1 generation. Supported by NIH grant R01-MH0104344, and the Veteran's Administration VISN 22 Mental Illness Research, Education, and Clinical Center.

Preconception Opioid Exposure has Bidirectional Effects on Morphine and Cocaine Reward in Offspring. Fair M. Vassoler[1], Anika M. Toorie[1], Delaney Teceno[1], Trevor Patton[1], Elizabeth M. Byrnes[1]. [1]Tufts University Cummings School of Veterinary Medicine. The United States is in the midst of an opioid epidemic, with abuse and misuse of prescription and illegal opioids increasing steadily over the past decade. A growing body of evidence describes that environmental exposures, such as opioids, can impact the physiology and behavior of subsequent generations. The current study was designed to test the hypothesis that maternal or paternal exposure to opioids prior to pregnancy alters abuse liability in subsequent generations. Female or male adolescent rats were administered morphine at increasing doses (5-25 mg/kg, s.c.) or saline for 10 days (P30-39). Animals then remained drug free for at least 3 weeks. During adulthood (P70-P90), animals were bred with drug-naïve partners. Male and female adult offspring (F1 animals) were tested for either morphine or cocaine self-administration acquisition, progressive ratio, extinction, and reinstatement (0.75-morphine and 0.5-cocaine mg/kg/infusion). In addition, mu-opioid receptor expression levels as well as β-endorphin peptide levels were measured in the nucleus accumbens and ventral tegmental area. There were both drug- and sex- dependent effects on all phases of the self-administration paradigm that indicate decreased morphine reward and attenuated relapse-like behavior and yet increased cocaine reward and enhanced relapse-like behavior in Mor-F1 animals compared with Sal-F1 animals. Additionally, both receptor and cognate peptide levels were altered in Mor-F1 animals. The results demonstrate that even limited opioid exposure during adolescence can have lasting effects across multiple generations. This work was funded by NIH NIDA R01 DA024567/A6, R03 DA034886, BBRF Young Investigator Award (NARSAD)

Transcriptional corepressor complexes in the regulation of neuronal plasticity. Francesca Telese[1], Patricia Montilla Perez[1], Florio, Ermanno[1], Iemolo, Attilio[1], Qi Ma[1], Michael G. Rosenfeld[2], Wen, Junneng[2], Rusu, Iulia[2] [1]School of Medicine, University of California, San Diego, La Jolla, CA, USA, [2]Howard Hughes Medical Institute, La Jolla, CA, USA, 3Division of Biological Sciences, University of California, San Diego, La Jolla, USA. Experience and environmental factors can leave their mark on genes via epigenetic mechanisms that drive sustained changes in gene expression, and in turn long-lasting behavioral outcomes. In neurons the fine-tuning regulation of transcriptional activation and repression is essential for learning and memory. Nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRT) are the most well characterized corepressor complexes. They mediate transcriptional repression for numerous transcription factors (TFs) and virtually all nuclear receptors, including glucocorticoid receptor (GR). This

complex facilitates the recruitment of histone deacetylases to impose repressive marks on regulatory elements bound by its interacting TFs. In our analysis, the conditional deletion of NCoR and SMRT leads to cognitive deficits. The genome-wide mapping of NCoR and SMRT by ChIP-seq suggest that they regulate transcriptional plasticity by modulating the activity of specific cis-regulatory enhancers. Our findings suggest that epigenetic mechanisms of gene transcription establish molecular memories that are essential for cognitive behavior. Funding acknowledgements: National Institute on Drug Abuse

1:30-3:30 **Symposium: The new kid on the block: Astrocytes in behavior and cognition.**
Chair: Mikhail V. Pletnikov, Johns Hopkins University School of Medicine. Co-Chair: Kathryn J. Reissner, University of North Carolina at Chapel Hill.

Cells That Tile Your Brain: astrocyte roles in neural circuits. Baljit S. Khakh. Department of Physiology, David Geffen School of Medicine, UCLA. Astrocytes have been studied for as long as neurons, with Cajal's beautiful drawings illustrating the morphology and diversity of both neurons and glia alike. However, twentieth century neuroscience was dominated by neuronal studies, because electrophysiology provided a precise way to study electrical activity. Thus studies of astrocytes, which represent ~50% of brain cells, lagged behind. The goal of my laboratory has been to use novel optical and genetic methods to study astrocytes, their roles in neural circuit formation and function, as well as how they regulate behaviors related to brain diseases. I will present our latest data on these topics.

Experience-dependent plasticity of astrocytes within the reward circuitry. Kathryn J. Reissner[1,2], Anze Testen[2], Kati L. Healey[1], Marian T. Sepulveda-Orengo[1]. 1Department of Psychology and Neuroscience, UNC Chapel Hill 2Neuroscience Curriculum, UNC Chapel Hill. Considerable evidence indicates important roles for astrocytes in function and dysfunction of the nervous system. Among these, astrocytes modulate, and are influenced by, neuronal and synaptic function. However, relatively little is known about the ways in which astrocytes respond to experience in vivo, and how these responses may influence both adaptive and maladaptive neural, synaptic, and behavioral plasticity. To address this question, we have developed an approach to utilize virally expressed membrane-associated GFP (AAV5 GfaABC1D-Lck-GFP) to evaluate structural features of astrocytes using high-resolution confocal microscopy. We have employed this approach to assess morphometric properties and synaptic colocalization of astrocytes within the male rat nucleus accumbens (NAc) following cocaine self-administration and extinction training. We find that NAc astrocytes from cocaine-extinguished rats exhibit significantly reduced surface area, volume, and synaptic colocalization, as compared to those from saline-experienced rats. We also find that astrocytes in the prelimbic prefrontal cortex and basolateral amygdala from the same rats are not affected. These results suggest the hypothesis that astrocytes may exert reduced modulation of synaptic processing in the NAc of cocaine-withdrawn rats. Importantly, changes in synaptic strength and resistance to induction of synaptic plasticity are well described in the NAc following cocaine experience. Among the ways in which astrocytes modulate synaptic strength and function is via generation and release of D-serine. Accordingly, in order to test the hypothesis that impaired astrocyte-derived D-serine contributes to the enduring maladaptive neural responses to cocaine, we tested the effects of D-serine augmentation on behavioral and synaptic measures in cocaine-withdrawn rats. We find that systemic D-serine augmentation reduces behavioral measures of cocaine seeking and increases NMDA receptor-mediated synaptic function in NAc medium spiny neurons. Ongoing studies are designed to more fully understand the mechanism by which augmentation of D-serine may influence relapse-related behaviors. Ongoing studies are also designed to investigate more fully the dynamics of cocaine-induced adaptations in astrocytes within the brain's reward circuitry. This work is supported by NIH grant R01DA041455 (KJR).

Astroglial MHCI following immune activation leads to behavioral and neuropathological changes. Kiyofumi Yamada[1], Akira Sobue[1], Norimichi Ito[1], Taku Nagai[1]. [1]Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine. In the CNS, major histocompatibility complex class I (MHCI) molecules are mainly expressed in neurons, and neuronal MHCI have roles in synapse elimination and plasticity. However, the pathophysiological significance of astroglial MHCI remains unclear. We herein demonstrate that MHCI expression is

up-regulated in astrocytes in the medial prefrontal cortex (mPFC) following systemic immune activation by an intraperitoneal injection of polyinosinic-polycytidylic acid (polyI:C) or hydrodynamic interferon (IFN)-γ gene delivery in male C57/BL6J mice. In cultured astrocytes, MHCI/H-2D largely co-localized with exosomes. In order to investigate the role of astroglial MHCI, H-2D or its soluble form (sH-2D) was expressed in the mPFC of male C57/BL6J mice using an adeno-associated virus (AAV) vector under the control of a glial fibrillary acidic protein (GFAP) promoter. The expression of astroglial MHCI in the mPFC impaired sociability and recognition memory in mice. Regarding neuropathological changes, MHCI expression in astrocytes significantly activated microglial cells, decreased parvalbumin (PV)-positive cell numbers, and reduced dendritic spine density in the mPFC. A treatment with GW4869 that impairs exosome synthesis ameliorated these behavioral and neuropathological changes. These results suggest that the overexpression of MHCI in astrocytes affects microglial proliferation as well as neuronal numbers and spine densities, thereby leading to social and cognitive deficits in mice, possibly via exosomes created by astrocytes. This work was supported by the following funding sources: KAKENHI Grant Numbers JP17H04031, JP17H04252, JP17H02220, JP16K15201, JP15H01284, and 25116515 from JSPS, the Private University Research Branding Project from MEXT, the SRPBS from AMED, Research on the Regulatory Science of Pharmaceuticals and Medical Devices from AMED, a Grant for Biomedical Research from SRF, the Astellas Foundation for Research on Metabolic Disorders, and The Pharmacological Research Foundation, Tokyo.

The region-specific role of astrocyte DISC1 in cognitive behaviors in mice. Terrillion, C.E.[1], Crawford, J.A.[1], Shevelkin, A.[1], Kim, S.H.[1], Fukudome, D.[1], Sawa, A.[1], Kamiya, A.[1], and Pletnikov, M.V.[1 1] Johns Hopkins University. Background: DISC1, which is expressed in both neurons and astrocytes, has been identified as a genetic risk factor associated with major psychiatric disorders, including schizophrenia. Neuronal Disc1 in the hippocampus and the prefrontal cortex has been implicated in cognitive function. However, the role of Disc1 in astrocytes, which have increasingly been shown to play a role in normal cognition, has not been evaluated. We hypothesized that decreased expression of DISC1 in astrocytes in the hippocampus or prefrontal cortex would impair cognitive behavior in mice. Methods: Mice were injected with the vector AAV1-GFAP::GFP-miR30-DISC1 (Disc1 KD) in the hippocampus or prefrontal cortex (PFC) to knock down DISC1 in astrocytes, or the scrambled control vector AAV1-GFAP::GFP-mir30-Ctrl (Ctrl). 2 weeks following injections, mice were tested in anxiety related measures including elevated plus maze and the open field, as well as several complex cognitive behaviors, including social interaction, Barnes maze and trace fear conditioning. Results: DISC1 KD in hippocampal or prefrontal cortex astrocytes did not alter locomotor activity or anxiety related behavior. DISC1 KD in hippocampal astrocytes impaired performance in the Barnes maze and reduced cue-dependent freezing in in trace fear conditioning. While DISC1 KD in PFC astrocytes also impaired performance in the Barnes maze, no significant effects of this KD were observed on cue-dependent freezing in trace fear conditioning. Additionally, we found that DISC1 KD altered GLT-1 levels in hippocampal astrocytes. Conclusion: Reduction of DISC1 expression in brain astrocytes leads to brain region-dependent deficiencies in complex cognitive tasks. Changes in astrocyte GLT-1 expression following DISC1 KD suggests that astrocytic dysfunction likely contributes to the cognitive deficits. Further understanding of the role DISC1 has in astrocyte function in relation to cognitive behaviors will allow us to improve treatment of cognitive symptoms in patients with major psychiatric disorders.

1:30-3:30 **Symposium: Corticotropin-releasing factor (CRF) modulation of cognition and motivation.** Chair: Sofiya Hupalo, University of Wisconsin, Madison. Co-Chair: Stan Floresco, University of British Columbia.

Corticotropin-releasing factor and stress affect cognitive flexibility through biogenic amine systems. Rita J. Valentino, National Institute of Drug Abuse. Corticotropin-releasing factor (CRF) alters activity of the locus coeruleus (LC)-norepinephrine (NE) and dorsal raphe (DR)-serotonin (5-HT) systems during stress. In turn these systems regulate cognitive flexibility through their cortical projections. The effects of CRF regulation of these systems were examined in male rats in tests of cognitive flexibility. When administered directly into the LC, CRF enhanced extradimensional set shifting in an attentional set shifting task at relatively low doses (6 ng) but this effect shifted to an enhancement of reversal learning with higher doses of CRF. These effects were mirrored by changes in prefrontal cortical (PFC) neuronal

activity as indicated by c-fos expression. The results are consistent with the concept of an inverted U-shape relationship between cortical norepinephrine and prefrontal cortical activity that is reflected in cognitive flexibility. In contrast to its effects on LC neurons, CRF inhibits and excites DR-5HT neurons through its action on CRF1 and CRF2 receptors, respectively. Because CRF1 is the predominant receptor on the plasma membrane in stress naïve male rats, moderate doses of CRF inhibit DR-5-HT neurons. Local injection of CRF (30 ng) into the DR of stress-naïve rats improved strategy shifting and this effect was associated with a predictable decrease in 5-HT extracellular levels in the PFC. Notably, in rats with a history of social stress that exhibit the strategy of resisting defeat, CRF receptors are redistributed such that CRF2 becomes predominant on the plasma membrane and CRF1 is internalized. In this population, the effect of CRF on DRN-5-HT neurons switches from inhibition to a CRF2-mediated excitation. Consistent with this, in these rats the effect of CRF switches from enhancing strategy shifting to enhancing reversal learning. These results highlight the potential for CRF regulation of DR-5-HT activity to determine cognitive strategies and the ability of stress history to shift this in association with coping strategy. Together these findings of CRF effects on LC-NE and DR-5HT systems underscore how cellular effects of CRF translate to distinct effects on cognitive processing that are dependent on level, localization, stress history and coping strategy.

Corticotropin-Releasing Factor (CRF) Modulation of Different Forms of Cost/Benefit Decision Making
Stan B. Floresco[1] 1 - Department of Psychology, University of British Columbia. Increased CRF activity is associated with stress-related psychiatric disorders such as depression and this may contribute to motivational and cognitive dysfunction associated with these conditions. The present series of experiments investigated how pharmacological increases in central CRF activity influences different forms of cost/benefit decision making, cognitive flexibility and choice behavior in situations involving uncertainty or ambiguity, assessed with a battery of translational rodent assays relevant to depression. Intracerebroventricular infusion of CRF reduced preference for larger, high cost rewards during performance of an effort-discounting task. However, these treatments had minimal effects on risk/reward decision making assessed with a probabilistic discounting task, where rats chose between a small/certain reward and larger, risky ones. On the other hand, increased CRF transmission altered cue-guided risk/reward decision making, where different auditory stimuli signaled the relative probability of obtaining a larger reward. Under these conditions, CRF treatments caused rats to display less profitable patterns of choice, in that they selected the risky option more often when cues signaled they were unlikely to be received. Lastly, we investigated how CRF may modulate the acquisition and performance of a probabilistic reversal learning task, where "correct" vs incorrect responses were rewarded on 80%/20% of trials. CRF treatments prior to acquisition did not increase erroneous responding but did reduce sensitivity to rewarded feedback. In comparison, in well–trained rats, these treatments increased/reduced sensitivity to reward and negative feedback, indicative of a deficit in medial prefrontal cortical function. Collectively, these data indicate that excessive CRF activity induces a complex array of effects on various forms of cost/benefit decision making and cognitive flexibility. In particular, increased CRF transmission robustly reduces preference for larger rewards associated with a greater effort cost, whereas its modulation of decisions involving reward uncertainty is more nuanced and dependent on the type of information used to guide choice. Funded by a grant from the Canadian Institutes of Health Research.

Sex differences in stress responses: A critical role for corticotropin releasing factor. Debra Bangasser Department of Psychology and Neuroscience Program, Temple University, Philadelphia, PA 19122, U.S.A. Psychiatric disorders with hyperarousal features, such as posttraumatic stress disorder and major depression, are more common in women. In contrast, disorders with cognitive deficits, such as schizophrenia and attention deficit hyperactivity disorder, are more common in men. Stress exacerbates the symptoms of these disorders, so sex differences in stress responses may drive differences in pathology. Here we will present data demonstrating sex differences in responses to the stress neuropeptide, corticotropin releasing factor (CRF), in rats. Our previous work found that the locus coeruleus-arousal system in females is more sensitive to CRF than in males. In contrast, recent work from our laboratory is finding that cognitive processes are more disrupted by CRF in males than females. Specifically, we determined that CRF disrupts sustained attention, the ability to detect intermittent and unpredictable events over time, in both sexes. However, females with elevated levels of ovarian hormones were protected from the negative effect of CRF on attention. Males

that lack high levels of these hormones would never benefit from their protection. We also found that spatial learning is disrupted by CRF in the medial septum (MS) differently in male than female rats. Males were more sensitive to this effect than females, such that a low dose of CRF in the MS that had no effect in females disrupted spatial learning in males. Collectively, these studies reveal that CRF disrupts arousal more in females and cognition more in males, suggesting that sex differences in sensitivity to CRF bias males and females towards different pathology.

Corticotropin-Releasing Factor (CRF) Modulation of Distinct Prefrontal Cortex (PFC)-Dependent Cognitive Processes. Sofiya Hupalo. University of Wisconsin-Madison, Madison, WI 53706. The prefrontal cortex (PFC) plays a critical role in higher cognitive processes that support goal-directed behavior. PFC-dependent cognitive dysfunction is implicated in multiple psychopathologies, including ADHD. Recent evidence demonstrates that corticotropin-releasing factor (CRF) receptor activation within the PFC impairs, while blockade of PFC CRF receptors improves working memory performance in rats. One possible source of CRF for the cognition-modulating receptors are local CRF-synthesizing neurons, long known to be prominent in the PFC. To examine whether these neurons modulate PFC-dependent cognition, we used a dual viral vector system to express hM3Dq-coupled designer receptors (DREADDs) in PFC CRF neurons. Chemogenetic activation of PFC CRF neurons using the DREADD agonist, clozapine-N-oxide (CNO), robustly impaired working memory performance. Conversely, chemogenetic suppression of PFC CRF neurons improved working memory. CNO had no impact on working memory in control virus-treated animals. Moreover, the working memory-impairing actions of PFC CRF neuronal activation were blocked by local infusions of a CRF antagonist (D-Phe-CRF, 100 ng). Collectively, these observations indicate the working memory actions of PFC CRF neurons involve local CRF receptor signaling. To examine whether PFC CRF neurotransmission modulates PFC-dependent cognition more broadly, we also examined the effects of PFC CRF manipulations in a signal detection test of sustained attention. Chemogenetic activation of PFC CRF neurons similarly impaired sustained attention. These actions were blocked with systemic (NBI 35965, 1 mg/kg), but not intra-PFC (D-Phe-CRF, 100 ng) administration of CRF antagonists. When administered alone and at a higher dose (2.5 mg/kg), the CRF antagonist, NBI 35965, significantly improved sustained attention performance. Collectively, these observations demonstrate CRF neurons in the PFC exert potent modulatory actions on multiple PFC-dependent cognitive processes via different projection pathways. Importantly, the cognition-enhancing effects of CRF antagonists in both tasks of working memory and sustained attention mimic the pro-cognitive actions of ADHD medications. As such, CRF antagonists may represent a novel pharmacological approach for the treatment of ADHD and other disorders associated with PFC-dependent cognitive dysfunction.

4:00-6:00 **Travel Award Blitz – Co-Chairs:** Stacey Rizzo, The Jackson Laboratory. Jill Silverman, MIND Institute, UC Davis School of Medicine.

Tracking the impact of early-life challenges on neurobiological correlates of social and stress responses in female adult rats. Kovalev, D., Brooks, M., Kent, M., & Lambert, K. Dept. of Psychology, University of Richmond, VA 23173. In humans, poverty and unpredictable environments have been associated with negative socioemotional developmental outcomes (Blair et al., 2016). Accordingly, the current study utilized a rodent model to assess the effects of restricted resources and unpredictable threats [simulating a poverty/low socioeconomic status (SES) model] on socioemotional neurobiological functions. In this model, female rats were raised in four different conditions defined by availability of materials for nest building [standard and restricted resources for control (CON) and low SES groups] and presence or absence of threat (predator odors) throughout the lactation period. Following weaning, offspring were pair-housed [according to their group assignments LOW SES/no threat; LOW SES/threat; CON SES/no threat; CON SES/threat, n=8 each group] in standard housing conditions for one year. Adult offspring were assessed in a social interaction task with a novel male rat and cage mate confined in a plastic container. Prior to the social task, rats were habituated to the arena to observe anxiety responses in a novel environment. Following behavioral testing, the brains were assessed for oxytocin (associated with social responsiveness). Behavioral results indicated that, during habituation, animals exposed to threat (T) exhibited higher rearing responses (p=.012; exploratory behavior). When a cage mate was placed in a plastic container, no threat (NT) animals exhibited more digging behavior (p=.03); threat animals exhibited more rearing behavior (p=.008). When a

novel male rat was placed in a plastic container, animals exposed to threat exhibited fewer responses directed toward the male (p=.009) as well as escape attempts from the cage (p=.021), yet they exhibited increased bouts of interrupted grooming (p=.007). Further, LOW SES animals exhibited more escape behavior (p=.017). A significant T/SES interaction indicated that rats raised in CON SES/NT conditions exhibited more nose-to-nose contact with the novel male (p=.021). Histology data revealed nonsignificant trend indicating increased oxytocin immunoreactivity in the supraoptic nucleus in no threat animals (p=.081). To assess stress responsiveness, corticosterone levels were measured. LOW SES/T condition rats exhibited the highest levels of corticosterone (p<.0005). In sum, behavioral and neurobiological data suggest long-term socioemotional effects in adult animals exposed to stressful conditions during the limited time of lactation.

Zebrafish responds to alcohol in the water before it reaches its brain. Benjamin Tsang [1], Steven Tran [2], Hayden Chow [3], Robert Gerlai [1,4] [1] Department of Psychology, University of Toronto Mississauga [2] Current address: Division of Biology and Biological Engineering, California Institute of Technology [3] Faculty of Science, University of Western Ontario [4] Department of Cell and Systems Biology, University of Toronto. The practicality and simplicity of alcohol administration in the zebrafish has made it an increasingly popular animal model for the study of alcohol abuse, addition, and tolerance. Despite the vast literature detailing the behavioral responses in zebrafish induced by alcohol treatment, none have explored whether or not the zebrafish can detect alcohol in their environment immediately after immersion. We argue that the ability for an animal to detect a drug in their surroundings before the mechanistic actions in the brain take effect is crucial for proper behavioral analysis and interpretation. In our study, we placed zebrafish singly into a 1.5 L tank filled with 1% alcohol solution, and recorded their behavior in high-definition. We subsequently analyzed the time course of behavioral changes over the 60-minute recording session that started with zebrafish being immersed in the alcohol solution, and discovered a time dependent effect of alcohol. In addition to using automated software to track zebrafish movements, we also employed manual observation-based quantification of behavior. Previously, alcohol was found, or was assumed not to have an immediate effect, suggesting no peripheral action and no immediate detection of this substance by zebrafish. Our findings disprove these past results and refute this assumption. At 1% v/v EtOH concentration, we found that within the first 3 minutes of exposure, zebrafish decreased their distance to bottom and increase their absolute turn angle. We suggest behavioral changes occurring before alcohol could reach the brain in an appreciable level (i.e. within 10-15 min after the start of immersion into alcohol solution) can only be due to peripheral effects, e.g. the fish sensing this drug in the water. Our results thus suggest that zebrafish are able to detect alcohol in their environment immediately after exposure, a finding that has implications for alcohol choice test paradigms.

Managing threat-reward conflict: Strategies of conflict-based decision making. Hector Bravo-Rivera[1], Patricia Rubio-Arzola[1], Paula Rodriguez-Aquino[3,] Albit Caban-Murillo[4] and Gregory J. Quirk[2]. Depts. of Psychiatry 2 and Anatomy & Neurobiology 1, Univ. of Puerto Rico School of Medicine, San Juan, PR 00936 2, Dept. of Biology, Univ. Of Puerto Rico, Bayamon, PR 009593, Univ. of Puerto Rico Rio Piedras, San Juan, PR 009364. The pursuit of reward and avoidance are two major behavioral motivators. Failure to balance these motivators results in maladaptive behaviors and may underlie many pathological conditions. Many studies focused on the neural substrate of avoidance, as well as reward seeking. However, little is known about the interaction between avoidance and reward-seeking circuits that result in adaptive behaviors. Previous work from our group has shown that rats learn to avoid foot-shocks by stepping onto a nearby platform when they hear a 30s tone that co-terminates with a 2s shock (Bravo-Rivera et al., 2014). In the platform-mediated avoidance task, rats continually press a lever to receive a reward pellet delivered on a variable interval schedule. Avoidance comes at a cost because the food lever cannot be reached from the platform. This cost is minimal, because food is also available during the inter-tone intervals. We modified the task to increase conflict by limiting food availability to the tone period. A light indicating food availability turned on at the same time as the tone-predicting shock. We observed three different behavioral responses to this conflicting situation. 10% (8/77) rats spent all the time on the platform and never pressed for food (avoidance-preferring subgroup). This lack of food seeking can be interpreted as the cost of excessive avoidance, and is not optimal. Finally, the remaining 18% (14/77) rats engaged in excessive food seeking showing little to no avoidance (food preferring subgroup). The increased number of footshocks received by the food-preferring group is the cost of excessive food seeking and is not optimal. In contrast, 72% (55/77) rats were able to

accommodate both food seeking and avoidance behaviors, by timing the occurrence of the shock (timer subgroup). Because the shock occurs 28s into the tone-light stimulus, these rats increased their food seeking during the early portion of the tone and avoided more as the tone progressed. Together, these findings revealed different naturally-occurring sub- groups, characterized by their contrasting behavioral response to threat-reward conflict. The approach of focusing on naturally occurring behavioral differences may provide insight into the circuits that drive decision making and their potential dysfunction in anxiety or addiction related disorders.

Localizing the role of Homer2 in regulation of methamphetamine reinforcement. C.N. Brown, E.K. Fultz, S. Ferdousian, S. Rogers, E. Lustig, T. E. Kippin, K. K. Szumlinski. University of California, Santa Barbara. Despite profound public health ramifications of methamphetamine (MA) abuse, neural mechanisms underlying the transition from early stages of drug use to addiction are poorly understood. Previous work indicates increased motivational valence and reinforcement for MA in Homer2 knockout mice, implicating this glutamate receptor related, post-synaptic scaffolding protein in neuroplasticity of early MA use. To probe these results with developmental and anatomical specificity, Homer2b expression was bidirectionally manipulated in the nucleus accumbens (NAC) core or shell using an adeno-associated viral vector (AAV) carrying either short hairpin RNA (shRNA) to knockdown, or complementary DNA (cDNA) to increase Homer2 expression. First, MA-induced place conditioning procedures were employed to gauge the effects of manipulating Homer2b levels upon MA's motivational valence. Then, operant conditioning procedures were utilized to examine changes in MA reinforcement and intake. We observed neuroanatomically selective effects of intra-NAC shRNA-Homer2b, with core infusions promoting and shell infusions attenuating MA reward sensitivity in C57BL/6J mice. Reversing the MA phenotype of Homer2 knockout mice, using AAV-cDNA, revealed inconsistent effects that conflict with data observed in knockout and shRNA-infused animals. Ultimately, these results indicate that while Homer2 seems to have a global inhibitory role in regulating MA reinforcement, its influence cannot be localized to the NAC sub-regions, implicating other sites of action and emphasizing the importance of investigating not only one isolated brain region, but rather the connectivity between regions. Therefore, future work will focus on characterizing the role of sub-circuits between the prefrontal cortex and the NAC in regulating MA reinforcement using chemogenetic techniques.

Hippocampal Cav1.2 channels mediate extinction of cocaine-associated memories via dopamine D1R activation. Caitlin E. Burgdorf[1,2], Delaney Fischer[1], Charlotte C. Bavley[1,2], Arlene Martinez-Rivera[1], Jonathan Hackett[1], Anjali M. Rajadhyaksha[1,2]. [1]Pediatric Neurology, Pediatrics, [2]Feil Family Brain and Mind and Research Institute, [3]Department of Psychiatry, [4]Department of Pharmacology, [5]Sackler Institute for Developmental Psychobiology Weill Cornell Medicine, New York, NY 10065. Cocaine addiction is characterized by persistent drug seeking that is often initiated following exposure to contextual cues associated with the rewarding effects of the drug. Extinction of these contextual cocaine-associated memories may act as a means to decrease relapse behavior, although the molecular mechanism underlying the learning of this new context-associated extinction memory is not well understood. Through the use of chemogenetic manipulations, we have found that dopamine D1R-expressing cells in the dorsal hippocampus are required for extinction of cocaine contextual memories, as measured by cocaine conditioned place preference. In an effort to identify downstream D1R signaling pathways recruited for extinction, we have found that extinction of cocaine CPP results in phosphorylation of the L type Ca2+ channel Cav1.2 at S1928, a site phosphorylated by PKA activated downstream of D1R. We also find that conditional knockout of Cav1.2 in D1R expressing cells attenuates extinction and is required in the dorsal hippocampus for cocaine CPP extinction. As Cav1.2 is associated with long term changes in activity-dependent gene expression, we performed molecular studies to investigate extinction-induced changes in Cav1.2-regulated transcription factors CREB and NFATc3 within the hippocampal nucleus. We found that extinction increased CREB, P-CREB and NFATc3 levels that were attenuated in extinction-resistant D1Cre, Cav1.2 KO mice. Future studies aim to investigate the role of Cav1.2 in gene expression changes within D1R-containing cells of the dorsal hippocampus during extinction of cocaine-associated memories, in addition to mapping the dopaminergic inputs into the dorsal hippocampus. In sum, these studies suggest that Cav1.2 within D1R-expressing cells of the dorsal hippocampus may mediate extinction of contextual cocaine-associated memories and represent a pathway that can be explored for future pharmacotherapies towards treatment of cocaine addiction.

The role of excessive corticotropin-releasing factor signaling in depression-related cognitive impairments under conditions of uncertainty. Courtney A Bryce[1], Alexandra J Adalbert[1], Mona M Claes[1], Stan B Floresco[1]. [1]University of British Columbia. Depression is a stress-related disorder characterized by a debilitating constellation of affective and cognitive symptoms. Though the etiology of depression is currently unknown, depressed patients show potentiated corticotropin-releasing factor (CRF) levels. Animal models of depression and CRF application in vitro produce alterations in dopamine (DA) neuron activity, demonstrating a potential role for CRF, perhaps via DA signaling, in mediating depressive symptoms. Indeed, in preclinical experiments, CRF administration produces a depressive-like phenotype in both simple and complex assays, indicating a possible role for CRF in dysphoric and amotivational symptoms of depression. Typically, the adverse outcomes associated with depression are due to affective symptoms, however, depression also causes substantial cognitive impairments. Therefore, our aim was two-fold: 1) to elucidate the potential role for CRF on a battery of complex tasks in which depressed patients demonstrate cognitive impairments, including cognitive flexibility and risk/reward decision-making, and 2) to clarify the actions of central CRF administration on VTA DA neuron physiology in vivo. To this end, we centrally administered CRF prior to training and following extensive training on a probabilistic reversal learning task. In this task, one lever is designated as 'correct' (80% reinforced) and the other lever is 'incorrect' (80% non-reinforced). After 8 consecutive correct choices, reward contingencies are reversed. CRF in this task facilitated cognitive flexibility, increasing reversals by increasing reward sensitivity and reducing negative feedback sensitivity when animals received extensive training, whereas reward sensitivity and negative feedback sensitivity were both reduced when CRF was administered at acquisition. Additionally, CRF improved decision-making when risk/reward information was internally represented, increasing choice of the more rewarding, but riskier, option when odds were good and reducing choice when odds were poor. However, when external cues guided choice behavior, CRF impaired decision-making, increasing choice of the more rewarding, but riskier, option when odds were poor. Collectively, these results reveal the complex effects of CRF on various aspects of cognition, some of which mirror those in depression. Future experiments will investigate the role of CRF on DA neuron activity in vivo to learn how CRF and DA might interact to mediate cognitive alterations.

Effect of DREADD-induced inhibition of cholinergic, glutamatergic and all PPTg neurons on sensorimotor gating. Niveen Fulcher[1], Erin Azzopardi[2], Cleusa De Oliveira[2], & Susanne Schmid[1,2] [1]Program in Neuroscience, [2]Department of Anatomy & Cell Biology, Schulich School of Medicine & Dentistry, University of Western Ontario, London, CA. The human brain is a complex organ that consistently receives an abundance of stimuli from the environment. Sensorimotor gating is a pre-attentive response that blocks out trivial information that would otherwise overwhelm the brain, and may be quantified through prepulse inhibition (PPI) of the acoustic startle response (ASR). Deficits of PPI are seen in an array of neuropsychiatric illnesses, such as autism spectrum disorder, schizophrenia and Fragile X Syndrome. Albeit underlying mechanisms of PPI and its deficits remain unclear, the mind-brain pedunculopontine tegmental nucleus (PPTg) is suggested as an integral modulator in the PPI pathway as it projects to the startle-mediating giant neurons of the caudal pontine reticular nuclei. Furthermore, the PPTg is comprised of three distinct neuron types- cholinergic, glutamatergic and GABAergic neurons. On one hand, literature emphasizes the cholinergic system as a crucial player of PPI, while others suggest that disruption of PPI in schizophrenia reflects an alteration in dopaminergic and glutamatergic neurotransmission. The ambiguity of this conserved mechanism roots our interest in the neuronal functions within the PPTg in PPI and its disruptions. The Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technique is a growing innovative chemogenetic procedure that involves the delivery of viral constructs intracranially and allows drug injections (i.e. Clozapine N-Oxide; CNO) to transiently activate/silence targeted classes of neurons. Here, we intracranially delivered bilaterally either a general-, cholinergic- or glutamatergic-inhibiting DREADD, or a control vector, into the PPTg of wild-type or Cre-ChAT male and female adult Long-Evans rats, respectively. Subjects recovered for 3 weeks and received an intraperitoneal injection of either the DREADD ligand clozapine N-oxide (CNO) or vehicle prior to PPI testing. Our findings suggest that transient inhibition of PPTg neurons disrupts PPI, while cholinergic inhibition does not significantly alter PPI. Moreover, preliminarily data suggests that glutamatergic silencing disrupts PPI. Immunohistochemistry verified the effectiveness of transfection and quantified co-localization of the DREADD receptors

with various neuronal markers. These data verify the usefulness of chemogenetic manipulation and shed light on the overlooked PPTg glutamate neurons in sensorimotor gating.

Stress during puberty has differential effects on impulse action and introduction of delays in reward contingencies. González-Martínez, L. F.[1,2], Lee, H. J.2, Delville, Y[2]. [2] Psychology Department, The University of Texas at Austin. Exposure to stress during childhood and adolescence has a wide range of effects impacting cognition and personality. Thus, early trauma is a risk factor for development of mental disorders during puberty. Our previous studies in hamsters showed that chronic social stress in early puberty results in enhanced impulsive action, in particular decreased action inhibition. In addition, previously stressed animals were found particularly aversive to delays in reward, observed as a rapid inhibition of response rate and interest in rewards. In order to broaden the effects of early stress on impulsive action, we analyzed changes in conditioned responses under varying delays between conditioning cue, addressing the capacity to wait to respond. Male golden hamsters were exposed daily to aggressive adults from postnatal day 28 to 42. Later in adulthood, animals were trained to respond to a light cue by nose-poking into a lid opening that triggered the delivery of food pellets reward in a five-choice-serial-reaction-time task (5-CSRTT). During testing, we introduced random and varying delays (2 to 40 seconds) between the lights in the conditioning chambers and in openings and we looked for premature nose-poking responses as an indicator of impulsive action. As delays grew longer, animals were more likely to perform premature responses. However, previously stressed animals were ca. 25% less likely to perform such actions by the longest delay. There were no significant differences between groups in accuracy, omissions or errors in any of the delays presented. Our results show opposite effects of early social stress on the two components of impulsive action: decreased action inhibition, but enhanced capacity to wait for a response. Our results also show differential responses to introduction of delays in the contingencies of reward: enhanced tolerance to delays between conditioning cues, but decreased tolerance for reward delays after a response. These studies while indicating complex neural changes underlying these behavioral consequences may help explaining the diverse patterns of impulsivity in personality disorders associated with early stress. These studies also point to early stress as a predictor of patient adherence to slowly progressing therapies. [1] Supported by predoctoral fellowship from COLCIENCIAS (Colombia).

Optogenetic inactivation of basolateral amygdala in young rats recapitulates aged rats' ability to delay gratification in an intertemporal choice task. Caesar M. Hernandez[1,4], Caitlin A. Orsini[2,3], Joseph A. McQuail[1,4], Matt M. Bruner[1], Chase Labiste[1], Alexa-Rae Wheeler[1], Tyler W. Ten Eyck[1], Sarthak Singhal[3], Sara N. Burke[1,4], C. Jason Frazier[3,4], Barry Setlow[2,4], Jennifer L. Bizon[1,4] Departments of [1]Neuroscience, [2]Psychiatry, [3]Pharmacodynamics and [4]McKnight Brain Institute, University of Florida, Gainesville Florida. Intertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. Such decisions require integration of existing reward representations (prior experience) with valuation of the organism's current wants and needs (incentive motivation). Prior studies in both humans and rodents show that relative to young adults, aged subjects are better able to delay gratification, and generally prefer large, delayed over small, immediate rewards. While the neural circuit and molecular changes that mediate these age differences in intertemporal choice are unknown, lesion studies consistently implicate the basolateral amygdala (BLA) in motivation and affective decision making. The current experiments used optogenetic approaches to determine the effects on choice behavior of temporally discrete BLA inactivation during an intertemporal choice task. Young adult (6 mo) and aged (24 mo) Fischer 344 x Brown Norway F1 hybrid (FBN) rats were surgically implanted with cannulae targeting BLA, into which pAAV-CaMKIIa-eNpHR3.0-mCherry (halorhodopsin) was delivered, and optic fibers were cemented. Rats were subsequently trained on an adjustable delay, intertemporal choice task in which preference for small vs. large rewards was evaluated in presence of increasing delays to large rewards. Upon reaching stable baseline performance, light-induced BLA inactivation was performed during deliberation (the period before choice) and outcome (after reward delivery). To control for effects of repeated laser stimulation on choice behavior, in other sessions, rats received discrete light-induced inactivation only during intertrial intervals (ITIs). In comparison to baseline and ITI, discrete BLA inactivation during deliberation *increased* young and aged rats' choice of the large, delayed reward, thus producing a pattern of choice performance in young that mimics that of aged rats. In contrast, BLA inactivation during the small reward outcome *decreased* choice of the large, delayed reward in young rats only. In a second cohort of behaviorally naïve young and

aged FBN rats, total RNA was extracted from the BLA, and RT-qPCR was used to assess basal expression of genes involved in glutamatergic and GABAergic signaling. GABAB receptor transcripts were reduced in the aged BLA, suggesting this brain region undergoes molecular changes to inhibitory signaling in aging. Finally, in a third cohort, young FBN rats were surgically implanted with cannulae targeting the BLA. Acute infusions of the GABAB receptor agonist, Baclofen, decreased choice of the large delayed reward in a dose-dependent manner. Together, these findings suggest that age-associated shifts in BLA excitatory/inhibitory signaling attenuate the influence of incentive motivation on cost-benefit decision making and contribute to the enhanced ability of older subjects to delay gratification.

Corticotropin-Releasing Factor (CRF) Modulation of Distinct Prefrontal Cortex (PFC)-Dependent Cognitive Processes. Sofiya Hupalo. University of Wisconsin-Madison, Madison, WI 53706. The prefrontal cortex (PFC) plays a critical role in higher cognitive processes that support goal-directed behavior. PFC-dependent cognitive dysfunction is implicated in multiple psychopathologies, including ADHD. Recent evidence demonstrates that corticotropin-releasing factor (CRF) receptor activation within the PFC impairs, while blockade of PFC CRF receptors improves working memory performance in rats. One possible source of CRF for the cognition-modulating receptors are local CRF-synthesizing neurons, long known to be prominent in the PFC. To examine whether these neurons modulate PFC-dependent cognition, we used a dual viral vector system to express hM3Dq-coupled designer receptors (DREADDs) in PFC CRF neurons. Chemogenetic activation of PFC CRF neurons using the DREADD agonist, clozapine-N-oxide (CNO), robustly impaired working memory performance. Conversely, chemogenetic suppression of PFC CRF neurons improved working memory. CNO had no impact on working memory in control virus-treated animals. Moreover, the working memory-impairing actions of PFC CRF neuronal activation were blocked by local infusions of a CRF antagonist (D-Phe-CRF, 100 ng). Collectively, these observations indicate the working memory actions of PFC CRF neurons involve local CRF receptor signaling. To examine whether PFC CRF neurotransmission modulates PFC-dependent cognition more broadly, we also examined the effects of PFC CRF manipulations in a signal detection test of sustained attention. Chemogenetic activation of PFC CRF neurons similarly impaired sustained attention. These actions were blocked with systemic (NBI 35965, 1 mg/kg), but not intra-PFC (D-Phe-CRF, 100 ng) administration of CRF antagonists. When administered alone and at a higher dose (2.5 mg/kg), the CRF antagonist, NBI 35965, significantly improved sustained attention performance. Collectively, these observations demonstrate CRF neurons in the PFC exert potent modulatory actions on multiple PFC-dependent cognitive processes via different projection pathways. Importantly, the cognition-enhancing effects of CRF antagonists in both tasks of working memory and sustained attention mimic the pro-cognitive actions of ADHD medications. As such, CRF antagonists may represent a novel pharmacological approach for the treatment of ADHD and other disorders associated with PFC-dependent cognitive dysfunction.

Altered emission of isolation-induced ultrasonic vocalizations in Cacna1c haploinsufficient rat pups Rukhshona Kayumova1, Theresa M. Kisko1, Moria D. Braun1, Rainer K.W. Schwarting1, Markus Wöhr1 1Behavioral Neuroscience, Faculty of Psychology, Philipps-University of Marburg, Gutenbergstr. 18, D-35032 Marburg, Germany. CACNA1C is a well replicated vulnerability gene for affective disorders. Furthermore, mutations in CACNA1C have been identified to cause Timothy syndrome, which features include autism spectrum disorder (ASD). The gene encodes an alpha-1 subunit of the voltage-dependent L-type gate calcium channel Cav1.2. Studies on the effects of Cacna1c deletions in genetically modified rodents on behavioral readouts with relevance to neuropsychiatric disorders are yet sparse. In particular, little is known about the effects of Cacna1c deletions on early developmental measures. Therefore, the aim of the present study was to describe the behavioral phenotype of Cacna1c haploinsufficient rat pups. To this aim, we used a newly generated Cacna1c rat model and compared Cacna1c heterozygous (+/-) pups to wildtype (+/+) littermate controls with specific emphasis on ultrasonic vocalizations (USV). Isolation-induced USV typically increase during the first week of life and decrease thereafter, giving rise to an inverted U-shaped pattern of call emission. Therefore, they were measured at postnatal days (PND) 5, 7, 9, and 11. Behavioral phenotyping further included developmental milestones, homing test, and a pup discrimination task that was utilized to test whether mothers display genotype-dependent pup preference. Results show that Cacna1c+/- rats are viable, with the expected 50/50 genotype and sex ratios being evident in Cacna1c+/+ x Cacna1c+/- breedings. At the behavioral level, the most prominent genotype

effect was seen in the emission of isolation-induced USV. While Cacna1c+/+ controls displayed the expected inverted U-shaped developmental call emission pattern, with call rate peaking at PND 9, call emission was severely delayed in Cacna1c+/- pups. Genotype effects on acoustic call features and developmental milestones were mild. In the homing test, both genotypes displayed a clear preference towards home cage bedding over fresh bedding material, reflecting intact social olfactory abilities and high levels of social motivation. Finally, mothers did not display genotype-dependent pup preference. Together, these findings indicate that Cacna1c is involved in the developmental regulation of pup ultrasonic calling. The observed delay is consistent with other rodent ASD models.

The effects of chemogenetic inhibition of prelimbic cortical inputs to the paraventricular nucleus of the thalamus on cue- and cocaine-induced drug-seeking behavior in sign-trackers vs. goal-trackers. Kuhn, Brittany[1]; Campus, Paolo[1], Klumpner, Marin[1]; Flagel, Shelly [1]University of Michigan. Relapse remains the biggest problem in the treatment of addiction, with rates as high as 90%. Cues associated with the drug-taking experience can turn into powerful motivators and elicit drug-seeking behaviors via Pavlovian learning. However, there is individual variation in the extent to which a cue can attain such motivational value and only when it is attributed with incentive salience does it gain inordinate control over behavior. To study the underlying neural mechanisms, we use an animal model that captures individual variation in the propensity to attribute incentive salience to reward-paired cues. In this model, sign-trackers (STs) are rats that attribute incentive salience to a reward-predicting cue, and will approach and manipulate the cue upon its presentation; whereas goal-trackers (GTs) assign only predictive value to the cue and go to the location of reward delivery upon cue presentation. Relative to GTs, STs are also more impulsive, have higher cocaine break-point and are more susceptible to cue-induced reinstatement of drug-seeking behavior. The paraventricular nucleus of the thalamus (PVT) has been recognized for mediating cue-motivated behaviors, including individual differences in the propensity for cue-induced relapse. However, the specific PVT circuitry mediating this variation in drug-seeking behavior remains unknown. The prelimbic cortex (PrL) sends dense projections to the PVT, and has been implicated in addiction-related behaviors. Using the ST/GT model, recent data from our lab shows that this pathway mediates the incentive value of reward cues. The current study used a dual-vector inhibitory (Gi) DREADD (Designer Receptors Exclusively Activated by Designer Drugs) to examine if inhibition of the PrL-PVT pathway differentially mediates cocaine-seeking behavior in STs vs. GTs. Rats were characterized as STs or GTs based on their behavior during a Pavlovian conditioned approach task and then underwent 2 weeks of cocaine self-administration followed by 4 weeks of abstinence and then extinction training. Prior to the tests for reinstatement, rats received either clozapine-N-oxide to activate the DREADD, or vehicle. Preliminary results suggest that inhibition of the PrL-PVT pathway increases drug-seeking behavior in STs during a cocaine-induced reinstatement test. These findings will further our understanding of the neurobiological mechanisms mediating relapse, and can lead to novel targets for the treatment of addiction. Funding provided by National Institute on Drug Abuse (NIDA) R01DA038599 (SBF) and T32DA007821 (BNK)

Drebrin regulates opiate-induced behavioral and structural plasticity in the NAc. Jennifer A. Martin1, Craig T. Werner[1], Ping Zhong[2], Zi-Jun Wang[2], Justin N. Siemian[1], Devin Hagarty[3], Rachael L. Neve[4], Jun-Xu Li1, Ramesh Chandra[5], Mary-Kay Lobo[5], Amy M. Gancarz[3], Zhen Yan[2], David M. Dietz[1] [1]Department of Pharmacology and Toxicology; Research Institute on Addictions, University At Buffalo [2]Department of Physiology and Biophysics, University at Buffalo [3]Department of Psychology, California State University, Bakersfield [4]Deparment of Brain and Cognitive Sciences, Massachusetts Institute of Technology [5]Department of Anatomy and Neurobiology, University of Maryland School of Medicine. Opiate addiction, a chronic relapsing disease, places a large societal and financial burden on our country. In particular, the fundamental issue for the therapeutic treatment of opiate addiction is the persistent drug craving, seeking, and high rates of relapse following drug abstinence. These behaviors are characterized by persistent behavioral and cellular plasticity in key regions of the mesolimbic dopamine system such as the nucleus accumbens (NAc), including structure and density of dendritic spines on Medium Spiny Neurons (MSNs). To date the cellular and molecular mechanism governing opiate-induced structural plasticity remains undetermined. Following heroin self-administration we find decreased expression of the essential actin-binding protein drebrin in the NAc, an effect that is transcriptionally regulated through HDAC2 binding on the drebrin promoter. Using viral mediated gene transfer, overexpression of drebrin attenuated, while CRISPR-Cas9

deletion exacerbated, heroin-primed, but not sucrose primed, relapse-like behaviors. In addition, drebrin overexpression produced a downward, while CRISPR-Cas9 produced an upward, vertical shift in a within-session dose-response curve; demonstrating drebrin regulates the reinforcing properties of heroin. Restoration of drebrin levels following heroin self-administration reversed the heroin-induced decreases in spine density and reduction in AMPA and NMDA receptor conductance. Taken together, these data demonstrate an essential role for drebrin in mediating the molecular mechanisms underlying opiate-induced behavioral and structural plasticity. More importantly, understanding these cellular responses will help lead to the therapeutic intervention for the prevention of relapse. Funding: NIDA R01DA037257, NIDA R01DA037257-S1 and NIGMS R25GM09545902

A single injection of losartan improves neurological outcome in male and female rats subjected to ischemic stroke. *Martinez-Jimenez S.M.[1], M. N. Gonzalez-Vega, N.M.[1], Ferchmin, P.A.[2], Martins, A.H.[3]; [1]Neuroscience, Universidad Central Del Caribe, Bayamon, PR; [2]Biochemistry, Universidad Central del Caribe, Bayamon, PR; [3]Phrarmacology, Universidad of Puerto Rico Medical Science Campus, San Juan, PR. Stroke is a leading cause of long-term disability and the leading preventable cause of disability in the United States. Ischemic stroke is caused by a blockade of blood vessels in the brain by a blood clot. The inflammation associated with this blockade causes loss of neurons, astrocytes and increased permeability in the blood brain barrier (BBB). Losartan is an angiotensin type 1 receptor blocker commonly used to decrease blood pressure but also has anti-inflammatory properties and in recent studies, has been observed to help maintain BBB integrity. But these studies have been performed with chronic administration of losartan; the efficacy of a single acute injection of losartan in stroke has yet to be quantified. We propose that a single dose of losartan will decrease the neuronal damage and at least partially restore BBB integrity in male and female rats subjected to ischemic stroke. To verify this hypothesis, we performed middle cerebral artery occlusion (MCAO) to induce an ischemic stroke in male and female Sprague Dawley rats weighing 250-300g. A single injection of losartan (1mg/Kg) or an equal volume of sterile saline was given intravenously as a pre-treatment or post-treatment. Neurological outcome and disability was measured using a modified neurological severity score test (NSS) 24hrs after stroke. NSS is comprised of sensorimotor tests including ability to walk, flexion of limbs, startle reflex, propioreceptive test, motor evaluation and presence of seizures, among others. Failure to preform a task increases the score and a higher score correlates to increased disability. For BBB integrity analysis, 2% Evans Blue (EB) dye was injected and dye infiltration measured inside the brain. Infarct damage was measured using tetrazolium chloride (TTC) solution and determining dead tissue in the brain. Losartan treatment shows a tendency to reduce infarct damage and BBB permeability in both sexes of losartan-treated rats when injected 5 min before stroke. This tendency is replicated in our preliminary data using rats injected 2hrs after the stroke onset. Regardless of injection time losartan treatment significantly improved neurological outcome in both sexes after stroke ($p<0.05$). Therefore, these results suggest that even a single injection conserves the neuroprotective effects of losartan against stroke and could prove to be a useful alternative therapeutic approach in stroke therapy.

The modulatory effect of rosmarinic acid in the rhythmic motor patterns of the lumbar spinal cord of neonatal mice. Mendez, Laura[1,4]; De Jesus, Kevin[2,4]; Garcia, Andrea[3,4]; Diaz, Manuel[1,4]. [1]Department of Anatomy and Neurobiology, University of Puerto Rico, Medical Science Campus. [2]Department Biology Science and Math, Interamericana University of Puerto Rico, Bayamon Campus. [3]Department Biology, University of Puerto Rico, Bayamon Campus. [4]Institute of Neurobiology, University of Puerto Rico, Medical Science Campus. Rosemary (Rosmarinus officinalis L.) is one of the most common household herbs, used as spices in a variety of foods, and employed in traditional medicine for its healing properties. Rosemary is a rich source of active antioxidant constituents such as phenolic diterpenes, flavonoids and phenolic acids. Caffeic acid and rosmarinic acid are its most important bioactive constituents. Rosmarinic acid is one of the most important and well known natural antioxidant compounds, which possesses neuroprotective effects in different models of neuroinflammation, neurodegeneration, as well as chemically-induced neurotoxicity and oxidative stress. These effects are beneficial for cancer patients, patients who suffered a spinal cord injury and for the potential treatment of other neurodegenerative diseases. Nevertheless, it has not been found or determined it this compound produces secondary effects in motor behaviors such as locomotion. Thus, we focused this study in assessing the effects of Rosmarinic Acid as a potential modulator of motor activity using the lumbar spinal cord of neonatal mice which possess

the neural network controlling locomotion. The evaluation of this potential modulatory effect was performed through electrophysiological techniques which included extracellular recordings of ventral nerves during a motor rhythm which can be elicited by the application of a mixture of serotonin (5-HT), NDMA (a glutamate analog) and dopamine. We measured changes in the peak amplitude, burst duration and cycle period of the recorded motoneuron-produced rhythm before, during and after the application of Rosmarinic acid at concentrations of 1µM and 100µM. So far, we have not observed significant changes in any of the parameters measured at low (1µM) or moderate concentrations (100uM). These results suggest that Rosmarinic Acid does not alter locomotor activity at these concentrations. Further experiments at higher concentrations will be conducted to assess any effects. These findings support the use of this compound or of the Rosemary plant as part of commercial drugs or natural supplements as possible neuroprotective agents.

Sex-dependent effects of two-hit stress on behavioral flexibility in rodents. Kelly M. Moench[1] and Cara L. Wellman[1]. Indiana University. 1Department of Psychological and Brain Sciences, Program in Neuroscience, and Center for the Integrative Study of Animal Behavior, Indiana University, Bloomington, IN, USA. Exposure to multiple stressful life events increases risk for many psychological disorders, including depression and anxiety. Women are at increased risk for these and other stress-related disorders, yet the mechanisms underlying this vulnerability are currently unknown. Animal models of stress typically focus on the immediate effects of chronic stress on brain and behavior. Using this approach, a paradoxical, male-biased vulnerability to stress has emerged, especially with regards to prefrontally mediated behaviors. For instance, male, but not female, rats exhibit stress-induced deficits in prefrontally-mediated tasks such as behavioral flexibility. We showed that chronically stressed male and female rats show differential response to a novel acute stressor in the days following chronic stress. When exposed to heterotypic acute stress following a 7-day rest period after chronic stress, female rats have an exaggerated response of the periventricular nucleus of the hypothalamus, whereas male rats do not. This suggests that exposure to chronic stress modulates later stress responsivity in a sex-dependent manner. This raises the possibility of sex differences in the cognitive ramifications of two-hit stress exposure, with females showing increased vulnerability. Here, we provide preliminary data investigating this possibility. We assessed whether prior exposure to chronic stress (restraint 3h/day, 10d) influences the effect of acute stress (30 min elevated platform stress) on behavioral flexibility using an attentional set-shifting task in male and female rats. Immediately following chronic stress, males had a deficit in behavioral flexibility specific to extradimensional shifting (EDS). This deficit was ameliorated following a 7-day post-stress rest period. Further, exposure to a heterotypic acute stressor after the 7-day rest period did not impair EDS in males. In contrast, female rats showed no deficit in set-shifting following chronic stress. Interestingly, deficits in EDS emerged in chronically stressed female rats after exposure to a heterotypic acute stressor 7 days post-chronic stress. Thus, while chronic stress may not have immediate deleterious effects on behavioral flexibility in female rats, it may alter the response to future stressors in a manner that induces maladaptive neurobiological and behavioral alterations. This pattern of results highlights the need to study sex differences in the lasting effects of chronic stress on brain and behavior.

Musical pleasure affects forward gait in patients with Parkinson's disease. K. Shin Park1, Chris J. Hass1, Bhavana Patel2, and Christopher M. Janelle1 1Department of Applied Physiology and Kinesiology, University of Florida 2Movement Disorders and Neurorestoration Center, University of Florida. Neurologic music therapy (NMT) has demonstrated clinical benefits in patients with Parkinson's disease (PD), especially improvement in gait disturbance. Most NMTs use an isochronous metronome pulse called rhythmic auditory stimulation (RAS) which ignores emotional and motivational benefits of music. Given that musical pleasure is associated with activation of the limbic-motor system, pleasurable music may produce beneficial alterations of gait compared to an isochronous beat. We sought to investigate how musical pleasure influences gait function in people with PD. Twelve individuals with mild to moderate level of idiopathic PD (age *M* = 69.5, *SD* = 4.96; 2 females; H&Y stage 1 – 3, on-med) completed 2-min walking trials while listening to emotionally-neutral (*isochronous beat*), self-chosen pleasant (*favorite*), and experimenter-chosen pleasant (*novel*) music selections, which were compared with walking at a natural pace (baseline). The tempo of all music selections was matched to the individual walking cadences measured during the baseline trial. The Ambulatory Parkinson's Disease Monitoring system (128_{Hz}, APDM Inc.) was used to record and analyze participants' stride and arm swing characteristics. Favorite music led

to faster gait velocity (1.17 ± .04$_{m/s}$) compared to baseline (1.11 ± .05, $p < .01$) and beat conditions (1.12 ± .04, $p < .01$). The increased velocity was largely driven by longer stride length (1.26 ± .05$_{m}$) compared to baseline (1.20 ± .05, $p < .01$) and beat (1.21±.05, $p < .01$). Arm swing peak velocity was greater during favorite (235.11 ± 35.08$_{degree/s}$, $p < .05$) and novel music conditions (238.32 ± 42.28, $p < .05$) compared to baseline (194.75 ± 31.30). Arm swing range of motion (ROM) was greater during favorite (54.18 ± 7.34$_{degree}$, $p < .01$) and novel music conditions (52.02 ± 7.44, $p < .01$) compared to baseline (44.38 ± 6.89). While novel music increased the variability of stride time (2.36±.18$_{CV\%}$, $p < .05$) and stride length (2.99±.21$_{CV\%}$, $p < .05$) compared to baseline (1.85±.11 and 2.40±.14), favorite music reduced arm swing ROM variability (13.41±1.24$_{CV\%}$, $p < .05$) relative to baseline (18.04 ± 2.76). Findings indicate that pleasurable music may have greater benefits for the improvement of gait amplitude and variability in patients with PD than an isochronous RAS, implying the potential role of the limbic-motor system in restoring and/or compensating for the impaired nigrostriatal pathway in PD.

Effects of ICI 182,780 on preference for cocaine in male rats. Jacqueline A. Quigley[1], Lahin K. Lalani[1], Benjamin G. Lipkin[1], & Jill B. Becker[1] [1]University of Michigan. There are sex differences in motivation for cocaine and cocaine-taking behavior in rodents. Susceptibility to addiction and addiction-like behaviors in females are modulated by estradiol. Research from the Becker laboratory has shown that estradiol enhances the cocaine-induced increase in dopamine in the dorsal striatum of female rats, but not male rats. This enhanced increase in dorsal striatum dopamine is thought to mediate the increased susceptibility of females to addiction and drug abuse. The role of estradiol, and other gonadal hormones, on addiction-like behaviors in males, however, is not well understood. Research from the Becker laboratory finds that estradiol does not enhance cocaine taking behavior of castrated male rats. The current experiment investigated the effects of estradiol receptor (ER) activation and inactivation on susceptibility to drug preference in intact males. Rats were initially given access to a three-compartment conditioned place preference (CPP) apparatus. A biased design was utilized to assign the initially non-preferred side with drug. For eight consecutive days, rats were conditioned every other day with cocaine (10 mg/kg, i.p.) or vehicle (saline) immediately before being placed into the apparatus. On day ten, animals had access to the entire chamber and their overall CPP was re-analyzed. Rats received intra-cannula administration of ICI182,780:Cholesterol (1:10) into dorsal striatum or nucleus accumbens constantly during conditioning and during the final test session. The control group received intra-cannula administration of Cholesterol only. Results indicate that ICI182,780 treatment in either location reduced the time spent in the drug-paired chamber on test day, compared to cholesterol treated males, or ICI182,780 or cholesterol treated females. These data indicate that ER manipulation in male rats, but not females, can affect CPP for cocaine. ICI182,780 is a non-specific G-protein ER (GPER1) agonist as well as an ER α/β antagonist, therefore, a follow up experiment was needed to tease apart these mechanisms. Experiments using G1, a GPER1 specific agonist, were conducted to determine whether the cocaine CPP can be modulated by GPER1 activation. Results will be presented at the meeting. These results indicate that while estradiol enhances drug-taking in females, in males it reduces CPP. These findings further our understanding of how ERs may play a crucial role in sex differences in the formation of drug preference.

Effects of experimental concussion by closed head injury on conditioned fear in rats. Melissa Rivera-López, M.A. and Demetrio Sierra-Mercado, PhD. Department of Anatomy & Neurobiology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico 00936. Traumatic brain injury (TBI) affects 4 million civilians and soldiers each year, many of who are diagnosed post-injury with neurological and cognitive dysfunction, such as excess fear. There are common mechanisms that contribute to the neurobiology of TBI and cognitive dysfunction. Notably, both can result in impaired learning and emotional regulation. Although epidemiological studies show a correlation between sustaining TBI and developing excess fear, animal studies show conflicting results. To evaluate the potential relationship between TBI and cognitive dysfunction, a biological link must be examined using reliable injury models and behavioral tests. We are testing the hypothesis that TBI would impair fear learned by Pavlovian conditioning in rats. Clinically, the most common type of TBI is concussion, in which an impact to the head plus angular acceleration produces neurological deficits and cognitive dysfunction. There are homologous brain regions in rodents and humans needed for the expression of fear memories. Dysfunction in the amygdala, hippocampus, and the medial prefrontal cortex (mPFC) underlie deficits in both rodents and humans with fear disorders. Notably, the effects of TBI to activity in homologous brain regions in the rodent are

unclear. To address this knowledge gap, we will mimic concussion in rodents using closed head injury (CHI) and sham injury. After recovery, we achieve delay conditioning by pairing an auditory stimulus (e.g. tone) with a foot shock, followed by subsequent tests for memory. Our preliminary results demonstrate that non-injured rats acquire a tone-shock association and express fear as indexed by a lack of movement save those related to breathing, known as freezing. To mimic the scenarios in which TBI occurs prior to or after exposure to an aversive event, we are assessing the delivery of CHI at one of two time points: 1) prior to fear conditioning, or 2) after conditioning. We aim to determine how CHI influences fear and assess activity in homologous brain regions in the rat. This work may lead to novel approaches for understanding and treatment of patients with TBI and fear disorders. Support provided by a RISE graduate fellowship to MR-L; a Young Investigator Grant from the Brain & Behavior Research Foundation (NARSAD) to DS-M; and RCMI8G12MD00760, UPR Medical Sciences Campus Chancellor's Office and School of Medicine Deanship.

Glutamatergic mechanisms in the inferior colliculus play a key role in paradoxical kinesia induced by appetitive 50-kHz ultrasonic vocalisations in rats. Luan Castro Tonelli[1], Markus Wöhr[1], Rainer K. W. Schwarting[1], Liana Melo-Thomas[1]. [1] Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, Gutenbergstrasse 18, 35032 Marburg, Germany. Immobile parkinsonian patients may be able to make quick movements, when excited by external stimuli. This is a phenomenon called paradoxical kinesia (PK) which refers to a sudden transient ability of akinetic patients to perform motor tasks they are otherwise unable to perform. The mechanisms underlying this phenomenon are unknown. However, in a previous study we proposed a new animal model to investigate PK in akinetic rats using species-relevant signals, namely rat ultrasonic vocalizations (USV) which are typical for social situations with positive valence like juvenile play or sexual encounters. Our aim in the present study was to uncover underlying brain mechanisms of PK. We focused on the inferior colliculus (IC) since it not only serves as an acoustic relay station, but can also modulate haloperidol-induced catalepsy. To test the role of the IC in PK induced by 50-kHz USV, male rats received intracollicular administration of NMDA (30nmol) or diazepam (10µg or 20µg) or its respective controls 10 min before haloperidol (0.5 mg/kg; ip). Rats were exposed to playback of 50-kHz USV, white noise, background noise or silence, 10 min each with 5 min intervals. The catalepsy test was measured during the bar test, which consists of placing the rat with its forepaws on a horizontal bar. The time until it stepped down was measured (maximum 600s). In animals which had received saline or vehicle microinjections into the IC, playback of 50-kHz USV significantly reduced haloperidol-induced catalepsy, and no such effects were observed in the case of other stimuli. However, the intracollicular administration of NMDA prevented the playback of 50-kHz USV effect on haloperidol–induced catalepsy. In contrast, although intracollicular diazepam microinjection potentiated the haloperidol-induced catalepsy, it did not affect the response to 50-kHz USV. Therefore, although both drugs microinjected into the IC potentiated haloperidol-induced catalepsy, they differ in their response to the 50-kHz USV playback. The agonist (NMDA) suppressed the effectiveness of the 50-kHz playback whereas the microinjection of the agonist GABA (diazepam) did not prevent the PK induced by the 50-kHz playback. These findings suggest that the neurobiological mechanisms underlying PK through the IC may be rather glutamatergic than GABAergic. Our approach to studying PK might be useful for uncovering the mechanisms behind this phenomenon and improving behavioural therapies for Parkinson's disease. We thank the Deutsche Forschungsgemeinschaft (DFG; ME4197/2-1) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; BEX 13557/13-0).

Relational memory in the scPCP mouse model for schizophrenia. Margarida Trigo[1], Dr. Jill Silverman[2], Prof. Joanna Neill[1] and Dr. John Gigg[1] [1]Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PT, UK; [2]UC Davis Mind Institute, 4625 2nd Avenue, Sacramento, CA 95817, USA. To help develop novel treatments for cognitive deficits in schizophrenia (SZ), the evaluation of novel compounds in SZ models by methods with high translational value to the clinic is required. The Bussey-Saksida touchscreen chamber provides such a translational method, as the touchscreen interface is analogous to that employed in SZ patients. An important cognitive deficit in SZ patients is in relational memory, with patients showing impaired capacity for transitive inference. The transitive inference (TI) task measures subjects' ability to make an indirect logical deduction after learning multiple overlapping discriminations between pairs of images in which one image is rewarded over the other. However, until now, transitive inference has not been tested in models for SZ using the touchscreen operant chamber. Here, we tested for TI deficits in the scPCP mouse

model of SZ, which displays both the negative symptoms and cognitive dysfunction phenotypes of SZ. First, we determined whether there was a sex difference in acquiring and performing touchscreen operant behaviour (visual discrimination, reversal and recall) and novel object recognition (NOR) memory in naïve c57BL/6J mice. Male and female mice performed similarly in operant tasks, however, interestingly female mice displayed stronger NOR performance. We, therefore, used female c57BL/6J mice in further experiments. Female mice were trained to criterion (75% correct) on overlapping premise pairs (A > B, B > C, etc.) to establish a reward hierarchy (A>B>C>D>E). Mice were then subject to PCP or vehicle (8 vehicle and 8 controls; 2 10ml/mg/Kg injections per day for 7 days). Cognitive effects of scPCP phenotype were tested by assessing NOR memory. All mice were then tested on novel pairs that either required transitivity (B vs D) or not (A vs E). Final results and analyses of the scPCP protocol on TI will be presented. This is the first report of acquisition and performance gender differences in the touchscreen chambers and also of deficits in transitive inference in the scPCP model, leading to a new view on the need to use both genders when testing in this manner and to the determination of a new deficit in the scPCP model, present in patients, useful when testing for new treatments.

Gonadal hormones mediate changes in adaptive choice and dopamine release in female rats. Yoest, KE[1], Shashlo, KE[1], Cummings, JA[1], Becker, JB[1]. [1] University of Michigan. In female rodents, sexual receptivity is coordinated by cyclic changes in the release of gonadal hormones. Increases in estradiol (E2) and progesterone (P) during proestrus and estrus not only induce ovulation, but also modulate behaviors that increase the probability that the female will find a mate and reproduce. This includes changes in receptive behaviors, such as lordosis, as well as appetitive or proceptive behaviors, including motivation. Interestingly, the direction of these changes in motivation is dependent on the type of reward that is being pursued. While induction of sexual receptivity by E2 and P increases motivation for access to a male, motivation for food is decreased. We have hypothesized that these concurrent changes in motivation facilitate adaptive choice across the estrous cycle. Females bias their choice in favor of a reproductive partner when fertilization is most likely to occur, but for food when copulation will not result in impregnation. In order to test this hypothesis, we developed a novel paradigm to measure motivated choice between a palatable food reward and access to a male conspecific. Ovariectomized, hormone primed females were trained to respond for both food and sex on a fixed interval (FI) schedule. After training, unprimed and primed females were tested in a chamber that allows them to choose between food and sex while still requiring responding on the FI schedule for each reward. From this we can not only determine the impact of hormone priming on female choice for food or sex, but also how this is reflected by changes in motivation for each reward, as measured by the average number of responses made during each interval. We have found that induction of sexual receptivity by hormone priming biases choice toward sex over food, and this change is reflected by a decrease in motivation for food but an increase in motivation for sex. We predict that E2 and P mediate changes in motivation via modulation of dopamine (DA) release in response to rewards and reward paired cues. To test this hypothesis, we are using fast scan cyclic voltammetry (FSCV) to measure how changes in motivation for food and sex are accompanied by changes in phasic DA release within the nucleus accumbens. This work provides a novel framework for understanding how release of gonadal hormones over the course of the estrous cycle modulates nucleus accumbens DA signaling, as well as how this can be related to adaptive behavioral choice in females. Funding: This study was funded by NFS IOS-1353263.

Role of neuroinflammation and amyloid in cognitive impairment in a mouse model of Alzheimer's disease. Shenghua Zhu1,2, Jun-Feng Wang1,2, Xin-Min Li3 1 Department of Pharmacology and Therapeutics, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, 2 Kleysen Institute for Advanced Medicine, Health Sciences Centre, Winnipeg, MB, Canada, 3 Department of Psychiatry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada. In Alzheimer’s disease (AD), both amyloid deposition and neuroinflammation appear in the early course and become notably conspicuous as disease progresses. However, the progression of neuroinflammation and its relationship with amyloid deposition and behavioural changes have not been characterized as many underlying mechanisms rarely occur in isolation. Methods: The present study will thoroughly characterize the behaviour of the APP/PS1 mouse model of AD, using a comprehensive test battery designed to assess a variety of behaviours. Using a crosssectional design, these behaviours will be assessed in mice at different ages. Brain

pathology measures for amyloid deposition and neuroinflammation are done post-mortem. Results: APP/PS1 mice exhibited significant learning deficits from the age of 5 month, which were aggravated at the later stages of life. However, the degree of memory impairment plateaus after 12 months. Histological analyses showed that an early appearance of amyloid plaques at 3 months of age with a linear progressive increase up to 22 months. This pronounced amyloid deposition was accompanied by a steady increase of the glial fibrillary acidic protein (GFAP) positive astrocytes and CD11b positive microglia up to the age of 9-12 months. Interestingly the expression levels of GFAP rose steeply from the age of 5 months to the age of 9 months and then stabilized at the age of 12 months which coincided with the observed pattern of learning deficits in APP/PS1 mice. Conclusions: These findings provided evidence that neuroinflammation might be involved in the development and progression of cognitive deficits in APP/PS1 mice, suggesting novel intervention and prevention strategies for AD.

Reward motivation in humans and its relationship to dopamine $D_{2/3}$ receptor availability: A pilot study with dual [^{11}C]-raclopride and [^{11}C]-(+)-PHNO imaging. Fernando Caravaggio[1,2], PhD, Gagan Fervaha[2], PhD, Caleb J. Browne[3,4], PhD, Philip Gerretsen[1,2], MSW., M.D., PhD, Gary Remington[1,2], M.D., PhD, Ariel Graff-Guerrero[1,2], M.D., PhD. [1]Research Imaging Centre, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario, Canada, M5T 1R8. [2]Department of Psychiatry, University of Toronto, 250 College Street, Toronto, Ontario, Canada, M5T 1R8. [3]Department of Psychology, University of Toronto, 250 College Street, Toronto, Ontario, Canada, M5T 1R8. [4]Section of Biopsychology, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario, Canada, M5T 1R8. Rodent studies suggest that DA signaling at $D_{2/3}$R receptors ($D_{2/3}$R) in the ventral striatum (VS) is critical for reward motivation. Whether this is also true in humans is unclear. Positron emission tomography (PET) studies in healthy humans have generally not observed a relationship between $D_{2/3}$R availability in the VS and motivation. We developed the "Mounting-Effort for Reward Task" (MeRT) to assess high motivational demand for, i) gaining money (%CS+), ii) losing money or avoiding electric shock (%CS-), and, iii) no reward (%Neutral). Receipt was contingent on participants making sufficient button responses relative to a "reward-threshold" determined by prior motor performance. This reward-threshold was dynamically increased if surpassed, making the task increasingly more difficult on every trial. The MeRT was preliminary validated in 29 healthy volunteers (mean age: 25.83±3.58; 15 female). In this sample, %CS+ and %CS- significantly correlated with different dimensions of self-reported apathy. In a sub-sample of 8 healthy volunteers (mean age: 25.75±1.91; 4 female), the MeRT demonstrated good test-retest reliability (%variance: 0.20%-2.61%). Seven healthy male volunteers (mean age: 31.14±5.43) completed the MeRT and provided both [^{11}C]-raclopride and [^{11}C]-(+)-PHNO PET scans to assess $D_{2/3}$R availability. %CS+ and %CS- were positively correlated with [^{11}C]-raclopride binding in the dorsal striatum. %CS+, %Cs-, and %Neutral were positively correlated with [^{11}C]-(+)-PHNO binding in the globus pallidus. Thus, increased expression of D_2R in the dorsal striatum, and D_3R in the globus pallidus, may be related to motivation for rewards. Larger PET studies are required to formally validate the MeRT and replicate our pilot findings.

Role of Cannabinoid CB1 receptors in mediating the long-term effects of adolescent chronic stress on the behavioral impairments following traumatic brain injury in adult rats. de la Tremblaye, Patricia B.[1]; Wellcome, Jody L[1].; Wiley, Kaitlyn M[1].; Cheng, Jeffrey P[1].; Bondi, Corina O[1]., Kline, Anthony E[1]. [1] Physical Medicine & Rehabilitation and Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, PA. Endocannabinoids are involved in the adaptation of the brain's response to stress through cannabinoid type 1 (CB1) receptors. CB1 activation has also been implicated in the neuropathology of traumatic brain injury (TBI), and has shown promise as a potential therapeutic target. However, it is unknown whether CB1 activation can reverse the long-term effects of adverse stress exposure during adolescence on adult TBI emotional and cognitive recovery. In the current study, adolescent male Sprague-Dawley rats were exposed to 4 weeks of chronic unpredictable stress (CUS) on postnatal day (PND) 30-60. After an additional 4 weeks of resting (PND 60-90), rats were anesthetized and receive either a controlled cortical impact of moderate severity (2.8 mm tissue deformation at 4m/s) or sham injury, immediately followed by daily pharmacological treatment with either CB1 agonist, ACEA (1 mg/kg), antagonist, AM251 (2 mg/kg), or vehicle (1 ml/kg), which were administered intraperitoneally for 7 consecutive days. After this week of recovery, rats were behaviorally assessed for anxiety in the elevated plus maze (EPM) and the open field test (OFT), sociability in the three-chamber social approach test, anhedonia in the sucrose preference

test (SPT), and cognitive performance in the novel object recognition (NOR) test, and Morris water maze (MWM). CUS exposure in adolescence increased time spent in the anxiogenic zones of the OFT and EPM and decreased sociability in sham rats, but improved NOR memory, and reduced time to reach the platform in the MWM in both sham and TBI groups, effects which were mediated by CB1 receptors. The results demonstrate that chronic unpredictable stress selectively impairs emotional responses, while providing some cognitive benefits, which may be context-dependent. Furthermore, CB1-mediated neurotransmission may effectively reverse the deleterious effects of adolescent -stress on behavioral recovery post TBI in adulthood.

COMTval158met polymorphism-modulated response to LPS is regulated through dopamine D1 signaling pathway: a first study linking COMTval158met polymorphism and immune mechanisms. J Deslauriers[1,2], X Zhou[1,2], VB Risbrough[1,2] [1] Department of Psychiatry, University of California San Diego, La Jolla, CA; [2] Veterans Affairs Center of Excellence for Stress and Mental Health, La Jolla, CA. Background: The catechol-O-methyltransferase (COMT) enzyme is implicated in the catabolism of dopamine and plays a key role in cortical signaling. The val158met single nucleotide polymorphism in the COMT gene has been associated with a greater risk of posttraumatic stress disorder (PTSD). In a “humanized” COMT mouse line, male Val/Val carriers, compared to Met/Met carriers, exhibited enduring inflammatory and anxiety-like responses to trauma exposure. Similar effects were found following a severe immune challenge, suggesting a role of COMTval158met-modulated inflammation in stress-induced behaviors. However, the mechanisms underlying the COMTval158met and its contributions to immune function and to trauma-induced inflammation remain unclear. Based on a previous study reporting dopamine D1 receptor-moderated systemic inflammation, we hypothesized that D1 signaling pathway regulates the COMTval158met-modulated response to immune challenge. Methods: The toll-like receptor 4 agonist lipopolysaccharide (LPS; 1 mg/kg, IP) or saline was administered in male Met/Met or Val/Val carriers to induce immune challenge. Simultaneously with LPS treatment and again for two following days, dopamine D1 agonist SKF-82958 (1 mg/kg/day, IP) was administered. One week, enduring anxiety-like behaviors were assessed in the open field and light/dark box tests. A composite avoidance score (Z score) across both tests was calculated for each animal. Results: Val/Val, compared to Met/Met, carriers showed the greatest increase of anxiety-like behaviors following LPS treatment. The D1 agonist SKF-82958 prevented the immune-induced behaviors only in Val/Val mice. Conclusions: These results indicate that dopamine D1-regulated immune pathways play a role in the COMTval158met-modulated response to immune challenge. Taken together with our previous data, these findings indicate that altered dopamine signaling underlie the alterations in immune and behavioral responses to trauma in COMTval158met carriers. Future work will examine the sex-dependent immune mechanisms related to COMTval158met and their modulation by the D1 signaling pathway.

Prefrontal function in fear and avoidance: From reaction to action. Maria M. Diehl[1], Christian Bravo-Rivera[1,2], Jose Rodríguez-Romaguera[1], Pablo A. Pagán-Rivera[1], Anthony Burgos-Robles[4], Jorge Iravedra-Garcia[1], Fabiola Gonzalez-Diaz[1], Gregory J. Quirk[1] 1Department of Psychiatry, University of Puerto Rico School of Medicine, San Juan, PR 00936 2Department of Neurobiology & Anatomy, University of Puerto Rico School of Medicine, San Juan, PR 00936. Much is known about the neural circuits of conditioned fear and its relevance to understanding anxiety disorders, but less is known about other anxiety-related behaviors such as active avoidance. Using a tone-signaled, platform-mediated active avoidance task, we observed that pharmacological inactivation of the prelimbic prefrontal cortex (PL) delayed the initiation of avoidance. However, optogenetic silencing of PL neurons did not delay avoidance. Consistent with this finding, inhibitory, but not excitatory, responses of rostral PL neurons to the tone were correlated with the initiation of avoidance. To oppose inhibitory responses, we photoactivated rostral PL neurons during the tone to maintain pre-tone firing rate. Photoactivation of rostral PL (but not caudal PL) neurons at 4 Hz (but not 2 Hz) delayed or prevented avoidance. These findings suggest that the initiation of active avoidance requires inhibitory neuronal responses in rostral PL, and underscores the importance of designing behavioral optogenetic studies based on neuronal firing patterns. Ongoing studies are examining whether projections of rPL to the ventral striatum or baslolateral amygdala are necessary for active avoidance using optogenetic techniques.

Stress Resilience: A State of Mind, A State of Gut. Anand Gururajan[1,2], Ana Paula Ventura-Silva[2], Josh Lyte[2], Thorsten Becker[2], Marcel van de Wouw[2], Marcus Boehme[2], Barbara Merckx[1], Niamh Wiley[3], Gerard M Moloney[1,2], Catherine Stanton[3], Ted G Dinan[2,4], John F Cryan[1,2] 1Department of Anatomy & Neuroscience, University College Cork, Ireland, 2APC Microbiome Institute Science, University College Cork, Ireland, 3Food Biosciences Department, Teagasc Food Research Centre, 4Department of Psychiatry & Neurobehavioural, University College Cork, Ireland. Background: The perception of stress exposure varies between individuals and depends on whether they are stress-resilient or stress-susceptible. These divergent phenotypes are underscored by a variety of central and peripheral physiological processes. The aim of our study was to identify these processes using a chronic stress paradigm in mice. In particular, we analysed gene expression in the bed nucleus of the stria terminalis (BNST), a relatively understudied structure in this context, and examined the faecal microbiome as a predictor of response to the stress paradigm. Methods: Male C57Bl/6 mice were subjected to chronic psychosocial defeat stress after which they were tested for social avoidance behaviour to classify mice as being either resilient or susceptible. The day before the first and the day after the last defeat session, tail blood samples were collected for analysis of plasma corticosterone and faecal samples were collected for 16S-rRNA sequencing. Mice were culled the day after behavioural testing. The BNST was dissected out from brains and RNA was extracted for sequencing. Results: Peripheral corticosterone levels were higher in stress-susceptible than stress-resilient mice after the social defeat stress paradigm. At baseline, the relative abundance of the specific families of gut microbes was higher in stress-susceptible than stress-resilient mice. RNA-seq analysis of the BNST revealed differential expression of several genes between groups. Furthermore, in resilient mice we observed increased expression of Pac1r, a receptor for pituitary adenylate cyclase activating peptide which has previously been implicated in the response to chronic stressors. Conclusions: Consistent with recent literature, we have shown that stress resilience is defined by a complex molecular and physiological profile which spans central and peripheral compartments. Our faecal microbiome data indicates that gut bacteria may be a predictive biomarker of stress response and that the upregulation of Pac1r in the BNST is a neuromolecular mechanism which is critical for the development of stress resilience.

Acetylcholine signaling in the ventral tegmental area regulates motivation to work for a desirable reward in an effort-based decision-making task. Joshua L. Haight, Durga J. Rathi, Eric J. Nunes, and Nii A. Addy. Department of Psychiatry, Yale University, New Haven, CT. Motivation to work for life-sustaining needs is a core feature of human and animal behavior. In addition, a lack of motivation (i.e. anhedonia) is a main symptom of depression. Studies utilizing rodents have demonstrated that dopamine signaling along the mesolimbic pathway, from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), is an essential component of the neurobiology underlying motivated and depression-like behaviors. While the role of dopamine in these behaviors has been demonstrated, the question surrounding what VTA inputs drive these behaviors remains. It has been hypothesized that cholinergic inputs into the VTA are critical for mediating motivated behavior. Recently, our lab and others have shown that cholinergic signaling in the VTA is a powerful regulator of both VTA dopamine cell activity and dopamine release in the NAc. In addition, our lab has demonstrated that cholinergic signaling in the VTA can regulate the ability of sucrose- and cocaine-paired cues to motivate reward-seeking behaviors, as well as depression-like behavior in the forced-swim test and elevated plus maze. Here, we examine the role of cholinergic signaling in the VTA in the effort-based decision making task. In this task, subjects have a choice between consuming freely available rat chow, or pressing a lever on a fixed-ratio 5 schedule to obtain 45mg sucrose pellets, a more highly desired reward. Importantly, the motivation to work for sucrose pellets in this task is dependent on dopamine transmission in the NAc, and this model has been suggested as a proxy for measuring the anhedonia-like symptoms of depression in rodents. In this study, we assessed the effects increased cholinergic tone, which is known to produce depressive symptoms in humans, on behavior in the effort-related choice task. We found that systemic administration of physostigmine (0.125 mg/kg) decreased lever responding, with no effect on chow consumption, in both male and female rats. In addition, preliminary data indicates that bilateral physostigmine infusion (2ug per side) directly into the VTA also decreased lever responding, while leaving chow consumption intact. These results suggest that cholinergic signaling, potentially in the VTA, regulates the motivation to work for a desirable reward, without reducing the drive to eat freely available chow. In addition, this work suggests that VTA cholinergic signaling might be an interesting target for regulating anhedonia.

6:30-7:00 **Early Career Award: Biological sex and parity: Potential moderators of exercise efficacy on brain health.**

Barha, Cindy K.; Rosano, Caterina; Best, John R.; Liu-Ambrose, Teresa

Biological sex and parity: Potential moderators of exercise efficacy on brain health. Cindy K. Barha1,2; Caterina Rosano3; John R. Best1,2; Teresa Liu-Ambrose1,2. 1Aging, Mobility, and Cognitive Neuroscience Lab, Department of Physical Therapy, University of British Columbia, Vancouver, Canada; 2Djavad Mowafaghian Centre for Brain Health, Vancouver, Canada; 3Department of Epidemiology, University of Pittsburgh, Pittsburgh, USA. Physical activity (PA) is a promising strategy for the promotion of brain health across the lifespan. Despite its overall therapeutic potential, substantial variation exists in PA efficacy at the individual level. Given the greater prevalence and faster progression of Alzheimer's disease in women compared to men, and known sex differences in brain architecture, analysis of sex differences in the relationship between PA and cognition, including underlying mechanisms, is warranted. To address this, we conducted secondary analyses of data from two studies: 1) PROMoTE – a randomized controlled trial of 6-month, thrice-weekly aerobic training (AT) in older adults with mild vascular dementia, and 2) Health ABC – a 10-year cohort study of 2873 older adults with retrospective PA measured through self-reported walking behaviour. A subset of 313 Health ABC participants underwent magnetic resonance imaging at year 10. Analysis of covariance and latent growth curve modeling were utilized to examine the interaction between sex and AT or PA, controlling for age, race, education, body mass index, diabetes, cardiovascular and cerebrovascular disease, brain atrophy, and total gray matter where appropriate. We focused on executive functions as meta-analyses suggest that PA has larger benefits for this cognitive domain. In both studies, we found that exercise (AT and PA) was significantly associated with greater executive functioning in females, but not males. Mechanistically, in the PROMoTE study AT increased levels of brain derived neurotrophic factor in females but not males. Furthermore, in the Health ABC data, maintenance of PA over time was related to larger dorsal lateral prefrontal cortical volume in females only. Together, these findings provide evidence that sex differences exist in the effect of PA on cognition as well as in the underlying neurobiological mechanisms, with females benefiting to a greater extent than males. We hypothesize that this may be related to long-lasting effects of parity on neuroplastic processes in females, possibly altering the way the female brain is able to respond to PA later in life. In support of this, I will present preliminary findings indicating that in older females the strength of the association between higher PA and greater cognitive function is modified by multiparity. This new knowledge of biological moderators of PA may foster development of personalized, tailored exercise recommendations to promote healthy brain aging.

7:00-7:30 **Outstanding Career Award: The Snark was a Boojum: Reconsideration in the context of Behavioral Neuroscience.**

Lambert, Kelly

The Snark was a Boojum: Reconsideration in the context of Behavioral Neuroscience. Kelly Lambert, Dept. of Psychology, University of Richmond, VA 23173 USA. Nearly 70 years ago Frank Beach, an American ethologist and pioneer in behavioral endocrinology, wrote an article entitled The Snark was a Boojum (inspired by a famous poem written by Lewis Carroll). As suggested by Carroll, hunting for snarks was a valuable endeavor; however, if a hunter's efforts ended up trapping a boojum, he/she was at risk of disappearing. This article served as a warning that researchers' narrow focus on a single animal model, the albino rat, could lead to the premature death of comparative psychology in the U.S. Recently, Macri and Richter (2015) reconsidered Beach's warnings in behavioral neuroscience research endeavors, concluding that the continued focus on very few species represents a persistent threat to the robustness of the field—we well as a barrier to the acquisition of desired translational effects addressing rising rates of psychiatric illness. Accordingly, recent efforts in our lab directed toward non-rodent species will be discussed; specifically, feral raccoons and semi-natural primate models are being used to determine the validity and robustness of relevant neurobiological responses in varying environmental contexts. Also of interest is a unique rodent species that is currently being considered for its potential

translational value for specific human phenotypes. New evidence emerging from investigations of this novel model animal will determine if it will ultimately be deemed a snark or boojum species.

Friday, June 29

8:00-9:00 **Keynote Speaker: Parental stress and epigenetic programming of offspring neurodevelopment.**

Bale, Tracy L., University of Maryland School of Medicine, Baltimore, MD, USA.

Parental stress and epigenetic programming of offspring neurodevelopment. Tracy L. Bale, Bridget Nugent, and Jennifer Chan. Departments of Pharmacology and Psychiatry, and Center for Epigenetic Research in Child Health and Brain Development, University of Maryland, Baltimore, MD. Parental lifetime exposures to perturbations such as stress, infection, malnutrition, and advanced age have been linked with an increased risk for offspring disease, including a strong association with neurodevelopmental disorders. While maternal insults during pregnancy can directly impact somatic cells and fetal development, the mechanisms by which lifelong parental experiences can alter germ cell programming and affect offspring brain development are just beginning to be examined. This session will discuss preclinical research that has begun to define the windows of vulnerability for both transgenerational and intergenerational programming and the unique epigenetic mechanisms involved. We have developed mouse models of both paternal and maternal life stress contributions to offspring brain development in which adult mice are exposed to chronic stress, prior to breeding or during pregnancy, as a sensitive windows important in development. In our mouse model of early prenatal stress (EPS), stress exposure during the first week of gestation imparts long-term developmental programming deficits in male, but not female, offspring resulting in hypersensitivity to stress, cognitive impairments, and alterations in metabolic programming. The placenta, a fetally-derived tissue reflecting fetal sex chromosome complement, acts as an arbitrator between the mother and fetus, providing necessary factors for early fetal neurodevelopment. We identified the X-linked, stress sensitive, nutrient sensor O-linked-N-acetylglucosamine (OGT) as a placental biomarker of prenatal stress. Genetic placental-specific reduction of OGT recapitulates the developmental and metabolic impairments associated with our mouse model. We found that OGT determines genome-wide sex differences in H3K27me3 and gene expression in placental trophoblasts. Our studies have currently focused on demonstrating the prenatal resilience for females that is programmed by the high levels of this transcriptionally repressive histone mark. In paternal transmission of life stress experience, our mouse model of paternal stress produces offspring with stress dysregulation. Paternal semen examined for changes in miRNA content established distinct expression patterns that were changed in both semen extracellular vesicles (EVs) as well as sperm from stressed mice. To test the relevance and potential mRNA targets of these miRNAs, we previously injected the miRNAs into single cell zygotes and found that the resulting offspring recapitulated the stress phenotype from paternal stress sires. We have demonstrated that the epididymal epithelial cells secreting miRNA-containing EVs were responsible for the programming that occurs at fertilization. Our recent studies have examined the role of glucocorticoid receptors in these epididymal cells in responding to paternal stress and altering the secreted EV miRNA content. Using genetic targeting strategies, we can rescue the paternal transmission of the offspring phenotype by reducing glucocorticoid receptors specifically in these cells. Overall, these results demonstrate that parental life experience can induce germ cell epigenetic reprogramming and impact offspring neurodevelopment, and may therefore offer novel insight into factors influencing disease risk. Identification of the specific miRNA in germ cells may point to unique biomarkers that could identify at-risk populations. Studies were funded by NIMH, and NIEHS.

9:30-11:30 **Symposium: Modifiable Risk Factors Contributing to Age-Related Memory Loss.**

Chair: Joseph A. McQuail, University of Florida, Gainesville.

Influence of age- and stress-related neuroendocrine dysfunction on executive functions and synaptic markers in prefrontal cortex. Joseph A. McQuail[1], Sahil Ghay[1], Matthew M. Bruner[1], Eric G. Krause[1], Barry Setlow[1], Deborah A. Scheuer[1], & Jennifer L. Bizon[1] [1]University of Florida, Gainesville, FL. Normal aging is associated with impaired cognition, including working memory supported by the prefrontal cortex (PFC). Our prior work strongly implicates altered PFC glutamatergic and GABAergic signaling in age-related working memory impairment. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis also accompanies the aging process and it has been proposed that the cumulative effects of stress and concomitant glucocorticoid exposure over the lifespan exacerbate neural changes that mediate the emergence of cognitive deficits. As the PFC is enriched in glucocorticoid receptors, ongoing work in our lab tests the hypothesis that age-related differences in HPA function associate with working memory ability and that chronic stress recapitulates adverse effects of aging on working memory and PFC glutamatergic/GABAergic signaling protein expression. First, we evaluated the relationship between working memory and circulating corticosterone (CORT) in aged rats. Young adult (4-6 mo) and aged (2 2-24 mo) rats were characterized for working memory ability using a delayed response task. As in our previous work, working memory in aged rats was less accurate than young, although aged performance spanned a broad range with some aged rats performing similar to young (unimpaired) and others performing worse than young (impaired). Basal CORT measured across the diurnal cycle was greater in aged rats than in young but this elevation was not associated with working memory. When challenged with a stressor (1 h restraint), stress-induced CORT was positively correlated with working memory performance of aged rats. Next, we determined the extent to which chronic variable stress can recapitulate the behavioral and molecular consequences of advanced aging. Young adult rats were exposed to a 21-day randomized schedule of twice-daily stressors including forced swims, water in cage, restraint stress and exposure to predator urine. Accuracy of working memory declined over the course of the regimen in chronically stressed rats compared to non-stressed controls. On the 22nd day, rats were sacrificed and PFCs dissected for molecular analysis. While markers affiliated with excitatory signaling (NMDARs, VGluT1) were not reliably changed by stress, expression of GABA(B)R1a, a presynaptic GABA autoreceptor, and VGAT, the presynaptic vesicular GABA transporter, were significantly reduced in the PFC of stressed rats. Collectively, our findings identify a causal role for stress in PFC GABA signaling alterations that could contribute to impaired working memory. NIH Grant F32AG051371 to JAM, NIH Grant R01HL076807 to DAS and NIH Grant R01AG029421 to JLB

A ketogenic diet improves biconditional association task acquisition and decreases anxiety-like behavior in young and aged rats. Abbi Hernandez[1], Keila Campos[1], Leah Truckenbrod[1], Brianna Moon[1], Quinten Federico[1], Sara N. Burke[1] [1]University of Florida. Cognitive impairment and increased incidence of anxiety often accompany advanced age. Although these age-associated disruptions can impair the ability to independently perform activities of daily living and decrease quality of life for older adults, the neurobiological mechanisms of these changes remain unknown. Among the first brain regions to be affected by aging are the medial temporal lobe (MTL) and prefrontal cortex (PFC), both of which must interact to support higher cognitive function. While many of the age-related biochemical alterations in MTL and PFC are uncorrelated, both of these structures are particularly vulnerable to age-related decreases in both neuronal glucose metabolism and mitochondrial function. These changes can affect cognitive processes, which require ATP bioavailability during task performance. While acute glucose application is restorative of several cognitive behaviors in rodents, long-term glucose consumption increases the risk of obesity and diabetes, which themselves eventually lead to cognitive impairment. Rather than trying to restore insulin/glucose signaling, an alternative approach for improving cognition in advanced age is to alleviate the dependence on glycolysis for cellular metabolism with a ketogenic diet (KD), which is a high-fat, low-carbohydrate diet that utilizes ketone bodies derived from fat for metabolism. Our previous work has shown that 12 weeks of a ketogenic diet (KD) can decrease body fat percentage and restore glutamate transporter protein levels within the hippocampus, suggesting that the KD may be beneficial for the aged brain. This current study aimed to see if the same diet could improve cognitive function on a task that is known to require MTL-PFC interactions. Young (4 month) and aged (20 month) rats were placed on a KD or control diet (CD) for 12 weeks prior to testing on several behavioral tasks, including a biconditional association task (BAT). Regardless of age group, rats on the KD outperformed CD rats on the BAT by making fewer mistakes on the object-in-place rule within the same number of training sessions. KD rats also exhibited less anxiety-like behavior, demonstrated by willingness to enter the open arm of the maze more readily than

CD rats. Furthermore, CD rats were significantly less likely to correctly make an object choice in the open arm than the closed arm, but KD rats were not. These data suggest that KDs are a therapeutic option for the treatment of age-related cognitive decline.

Systemic inflammation mediates age-related cognitive deficits. Tian Lin[1], Gene Liu[1], Yenisel Cruz-Almeida[2, 3], & Natalie C. Ebner[1, 2, 3] [1]Department of Psychology, University of Florida, Gainesville, FL, USA; [2]Department of Aging and Geriatric Research, Institute on Aging, University of Florida, Gainesville, FL, USA; [3]Center for Cognitive Aging and Memory, Department of Clinical and Health Psychology, University of Florida, Gainesville, FL, USA. The association between systematic inflammation and cognitive deficits is well-documented. Further, previous studies show that systemic inflammation levels increase with age. The present study took a novel approach by examining the extent to which systematic inflammation levels mediated age-related cognitive decline. Forty-seven young and 46 generally healthy older adults completed two cognitive tasks measuring processing speed and short-term memory, respectively. Serum concentrations of three inflammatory biomarkers (IL-6, TNF-α, CRP) were measured in each participant. Both cognitive measures showed age-related deficits. In addition, levels of IL-6 and TNF-α were elevated with age. IL-6 partially mediated the difference in processing speed between the young and the older participant age group; there was no mediation effect for TNF-α and CRP. Considering chronological age, IL-6 also partially accounted for age-related impairment in processing speed within older but not young participants. No effects were found for short-term memory. Evidence from this research supports the role of inflammatory processes in age-related cognitive decline. Potential underlying mechanisms of this mediation effect and differences in inflammatory influence on specific cognitive functions are discussed. Acknowledgements. This work was supported by the Department of Psychology at University of Florida, the McKnight Brain Research Foundation, and the University of Florida Center for Cognitive Aging and Memory, a University of Florida Clinical and Translational Science pilot award (NIH/NCATS; UL1 TR000064), and a Scientific Research Network on Decision Neuroscience and Aging pilot award (NIH/NIA, R24 AG039350) to NCE. While working on this project, NCE was in part supported by the NIH-funded Claude D. Pepper Older Americans Independence Center (P30AG028740).

9:30-11:30 **Symposium: Reactivation-induced memory destabilization: A gateway to memory change with significant therapeutic implications.** Chair: Boyer Winters, University of Guelph.

Inducing prediction error to trigger reconsolidation. Exton-McGuinness, Marc; Lee, Jonathan. University of Birmingham, B15 2TT, United Kingdom. Reconsolidation is now well-accepted as the natural mechanism for updating memories in our brains. Modifying a memory's content first requires destabilisation of that trace, typically achieved through some form of retrieval event. Once destabilised form, a memory is vulnerable to amnesia – often induced experimentally via blockade of the NMDA receptor – resulting in weakening of the associated behavioural response. The ability to erase memories that underpin maladaptive behaviours in a targeted fashion is of great therapeutic value, particularly in treatment of PTSD and addictions. However, several studies exist in which negative results have been found. This has led to the concept of 'boundary conditions' which constrain reconsolidation – older and stronger memories are thought more difficult to destabilise. This is a challenge for clinical translation where well-established memories are the norm. Based on the hypothesis that reconsolidation mediates updating of memories, we set out to explore whether strong memories can be destabilised following generation of a prediction error signal. In the case of pavlovian memory we found the parameters necessary to destabilise memory are proportional to the amount of training received, while instrumental memories were found to undergo reconsolidation following a change in reinforcement contingency. Together these findings help us understand the conditions under which memories can be made labile, opening up exciting new possibilities for clinical therapy – as well as future challenges on the horizon.

Retrieval-extinction without destabilisation still reduces recovery of fear. Emma N Cahill[1,2], Melissa A Wood[1,2,] Barry J Everitt[1,2] & Amy L Milton[1,2] 1 Department of Psychology, University of Cambridge, CB2 3EB, UK. 2 Behavioural and Clinical Neuroscience Institute, Cambridge, CB2 3EB, UK. A novel therapeutic strategy is to disrupt a fear memory by performing

extinction within the reconsolidation window, after a memory has been retrieved and destabilised. In contrast to the use of 'amnestic agents' targeting specific neurochemical processes, this procedure may potentially reduce symptoms of disorders such as PTSD by using only behavioural interventions. This 'retrieval-extinction' procedure has been investigated to reduce the impact of fear or drug-associated memories on behaviour. However, the mechanisms that underlie the 'retrieval-extinction' effect remain unclear. There was no direct demonstration in the original paper that the memory destabilised, nonetheless the early interpretations of the effect were that retrieval-extinction acts through reconsolidation interference. Despite the mechanisms of the effect remaining unclear, dozens of subsequent studies adapted the protocol to test whether 'retrieval-extinction' could affect appetitive or aversive memories in humans and in rats, but with varying levels of successful replication. If the effect depends on destabilisation of the original memory, then it would be expected that prediction error would be key to observing the effect. Using pavlovian fear-conditioned rats and targeted pharmacology, we found that remarkably the retrieval-extinction effect can be observed when there is explicitly no prediction error or if destabilisation is pharmacologically prevented. This goes against the original interpretation of the mechanism underlying this effect, namely, it does not always depend on reconsolidation mechanisms. Instead, we argue that an extinction-based account may be more appropriate to explain the actions of cued-fear retrieval extinction. We are currently performing molecular analysis to disentangle whether molecular markers of extinction are geared up by the retrieval-extinction procedure versus extinction alone. Together, these data suggest that retrieval-extinction does not require memory destabilisation, since behavioural or pharmacological interventions that prevent destabilisation did not disrupt any capacity to attenuate fear. Funding acknowledgements: This work was conducted within the Behavioural and Clinical Neuroscience Institute (BCNI), a joint initiative funded by the Wellcome Trust and the UK Medical Research Council, in the Department of Psychology at the University of Cambridge. This work was funded by a UK Medical Research Council programme grant (no. G1002231) awarded to B.J.E. and A.L.M and BBSRC Anniversary Future Leaders Fellowship (BB/M01407X/1) awarded to E.N.C. M.A.W was supported by a doctoral training grant from the BCNI. A.L.M. is the Ferreras-Willetts Fellow in Neuroscience at Downing College, Cambridge. Financial Interests or conflicts of interest: ENC is currently receiving funding from Boehringer Ingelheim Pharma GmbH & Co. for a project unrelated to this work.

Acetylcholine as a novel key to memory destabilisation: Implications for the updating of established memories in healthy and dysfunctional brains. Boyer Winters. University of Guelph, Ontario, Canada. Reconsolidation theory states that memories can re-enter a labile state following reactivation. However, boundary conditions, such as the strength or age of the memory, strongly influence the likelihood of trace destabilisation. Interestingly, boundary conditions can be overcome if reactivation occurs in the presence of salient novel information, consistent with a role for reconsolidation in adaptive memory modification. Given the permissive role of memory destabilisation in this process, it is essential that we understand the underlying neural mechanisms. Using the spontaneous object recognition (SOR) paradigm for rats, we have shown that relatively remote or strongly encoded object memories are most likely to destabilise when reactivated in the presence of explicit novelty, and this effect relies on cholinergic signalling at M1 muscarinic receptors in perirhinal cortex (PRh). Furthermore, our findings suggest that M1 receptor stimulation in PRh induces intracellular calcium release via IP3 receptor activation; this could promote post-synaptic protein degradation by the ubiquitin proteasome system (UPS), which is involved in destabilising contextual fear memories in the hippocampus. Indeed, UPS activation is also necessary for M1-induced object memory destabilisation in PRh, and we are currently investigating the potential role of CaMKII in this process. We have also developed a variant of the SOR task to study the mechanisms underlying object memory modification directly. Specifically, when rats are placed into a different context shortly after object memory destabilisation, they subsequently treat that object-context configuration as familiar even though the object was never explored in the context. This effect is reactivation- and time-dependent and provides support for the memory modification hypothesis of reconsolidation. We are currently evaluating the role of M1 receptors in this phenomenon. This work should help to specify the behavioural conditions and neural mechanisms involved in modification of long-term memories, a process that likely influences mnemonic flexibility throughout the lifespan. Given the prevalence of cognitive disorders characterized by cholinergic system dysfunction, this research could have significant

clinical relevance. If these effects are generalizable, established cholinergic drugs could also be used as adjunct therapies to treat conditions such as PTSD, which derive from strong, maladaptive memories. Supported by NSERC.

Modifying human episodic memories: reactivation as a precondition for change. Almut Hupbach, Iiona Scully. Department of Psychology, Lehigh University. Upon reactivation, long-term memories return to a plastic state in which they are vulnerable to a variety of interventions and require de novo protein synthesis to re-stabilize. This has been demonstrated numerous times in animal conditioning paradigms, but it remains controversial whether similar processes operate in human episodic memory. In my talk, I will review the literature on reactivation-induced modification in human episodic memory. I will describe the results of a recent meta-analysis showing that reactivation makes episodic memories susceptible to both physiological and behavioral interference manipulations. When applied shortly after reactivation, these manipulations alter the amount of information that can be retrieved from the original episode. This effect is more pronounced for remote memories and memories of narrative structure. Additionally, new learning following reactivation often leads to the updating of reactivated memories with new information. These findings support a dynamic view of long-term memory by showing that memories can be changed long after they were acquired. Different theoretical perspectives of these finding and the unique challenges this area of research faces will be discussed.

9:30-11:30 **Symposium: Social transmission of information in mammals: Key insights from rodents and non-human primates.** Chair: Aleksandra Vicentic, National Institute of Mental Health. Co-Chair: Anthony Noel Burgos-Robles, Massachusetts Institute of Technology.

Observational fear learning requires cortico-amygdala transfer of socially-derived information. Anthony Burgos-Robles[1],*, Stephen A. Allsop[1],*, Romy Wichmann[1],*, Fergil Mills[1],*, Chia-Jung Chang[1], Ada C. Felix-Ortiz[1], Alienor Vienne[1], Anna Beyeler[1], Ehsan M. Izadmehr[1], Gordon Glober[1], Meghan I. Cum[1], Johanna Stergiadou[1], Kavitha K. Anandalingam[1], Kathryn Farris[1], Praneeth Namburi[1], Christopher A. Leppla[1], Javier C. Weddington[1], Edward H. Nieh[1], Anne C. Smith[1], Demba Ba[1], Emery H. Brown[1], Kay M. Tye[1]. 1 Massachusetts Institute of Technology, Department of Brain and Cognitive Sciences, Picower Institute for Learning and Memory, Cambridge, MA 02139, USA. * Denotes equal contribution. Learning about danger through observation of conspecifics undergoing the actual danger is critical for survival. For instance, observational learning can allow organisms to learn aversive associations in the environment, such as certain smells or colors predicting predators or poisonous food, without direct experience. The ability to learn through observation has been associated to reciprocally interconnected brain regions in the limbic system, such as the anterior cingulate cortex (ACC) and the basolateral amygdala (BLA). However, it is not well understood how aversive associations are encoded in this limbic network during observational learning. To investigate the neural substrates of observational learning in the ACC-BLA network, we performed electrophysiological single-unit recordings in mice observing cagemate conspecifics undergoing associative fear conditioning in which a compound tone-light cue predicted electric shock. We also combined neural recordings with optogenetic techniques to either identify BLA-projecting ACC neurons, or to record the activity of BLA neurons while inhibiting ACC input. We also used optogenetic approaches to inhibit either ACCàBLA to BLAàACC projections during either observational cued fear conditioning or during other ethologically-relevant social behaviors such as avoidance of aggressive and potentially threatening CD-1 mice. Our results support a model wherein the ACC represents socially-derived aversive information, and that this information is transmitted to the BLA wherein observational aversive associations are formed. This neural process could endow aversive value to environmental cues without direct experience of aversive outcomes.

A putative role of the primate amygdala in the receiving-emitting cycle of facial expressions. Katalin M. Gothard, Prisca E. Zimmerman, Jeremiah K. Morrow, and Andrew J. Fuglevand. The University of Arizona, College of Medicine, Dept. of Physiology. The primate amygdala is a cluster of interconnected nuclei involved in detecting and decoding social signals from the environment, and in generating appropriate social responses. We, and others, have shown that neurons in the macaque amygdala respond selectively to faces and facial expressions. Face cells jointly encode identity and facial

expression, which is ideal for representing the emotional significance of facial expression in a hierarchically fluid society, where individuals often gain or lose social status. Macaque monkeys, like humans, allocate considerable time to looking at the eyes of conspecifics. When monkeys look at eyes, a specialized class of cells called eye cells in the amygdala become active. In monkeys, eye contact triggers the reciprocation of facial expressions. Indeed, the longer the eye contact between individuals the more likely that an exchange of facial expressions will take place. The amygdala may contribute to the production of facial expression by reporting to facial motor cortical areas the current status of the face. Specifically, cutaneous receptors in the face become stimulated during the display of facial expressions and input from these receptors activates tactile neurons in the amygdala. The amygdala therefore responds to the facial communicative signals of the self (proprioception via cutaneous inputs) and of others (visual responses to facial signals) potentially closing a sensory motor loop involved in the emitting-receiving cycle of facial expressions.

Social dominance status predicts vicarious fear learning from conspecifics in rats. Marie-H. Monfils & Carolyn E. Jones. Department of Psychology, University of Texas at Austin. This talk will focus on the role of social factors in social transmission of information. Utilizing a modified demonstrator-observer paradigm (fear conditioning by proxy) that allows for free interaction between subjects, we show that social dominance hierarchy is predictive of the potency of social fear transmission, with subordinate rats displaying increased fear responses after interacting with a fear conditioned dominant rat during fear retrieval. We found that 1) the majority of standard laboratory cages have an easily identifiable social hierarchy, 2) subordinate rats learn to freeze more when observing and interacting with a more dominant animal, and 3) play fighting indices of the social relationship correlate with the occurrence of ultrasonic vocalizations during social transmission sessions, freezing displayed after exposure to a fearful conspecific, and the neuroendocrine (corticosterone) response to a vicariously conditioned stimulus.

Observational fear as an enhancer of inhibitory avoidance. Alexei Morozov[1,2,3], Wataru Ito[1]. 1Virginia Tech Carilion Research Institute, Roanoke, Virginia, USA; 2School of Biomedical Engineering and Sciences, Virginia Tech, Blacksburg, Virginia, USA; 3Department of Psychiatry and Behavioral Medicine, Virginia Tech Carilion School of Medicine, Roanoke, Virginia, USA. Social signals are strong triggers and modulators of various behaviors in many organisms. Some signals elicit immediate behavioral responses whereas others cause long-lasting adaptations. The known long-lasting adaptations include learning or unlearned changes in emotional state. Using mice, we found that a brief exposure of an observer mouse to a conspecific demonstrator that is receiving electrical footshocks acts as a primer that causes a stronger learning of the inhibitory avoidance task, performed on the observer at a later time. Our electrophysiological analyses suggest that a neuronal trace from that primer, responsible for the better learning, resides in the prefrontal-amygdala pathway, in the form of silent synapses, which enable a stronger plasticity of that pathway during the consolidation of inhibitory avoidance memories. Supported by NIH grant R21MH10797070

1:30-3:30 **Symposium: Mechanisms underlying memory consolidation and retrieval.** Chair: Ryan LaLumiere, University of Iowa. Co-Chair: Janine Kwapis, University of California, Irvine.

Specific projections from the amygdala modulate the consolidation for different aspects of memory. Ryan T. LaLumiere[1], [1]University of Iowa. Although much evidence indicates the basolateral complex of the amygdala (BLA) influences the consolidation for many different kinds of memories, the circuitry mechanisms underlying this modulatory influence have not been clear. In fact, whereas the BLA modulates the consolidation for memories as diverse as spatial and cued-response water maze, conditioned taste aversion, and inhibitory avoidance, other brain regions play more selective roles. In recent years, our work has begun to tease apart the circuits by which the BLA engages in memory modulation and suggests that different efferent projections influence only specific aspects or types of memories. Using optogenetic approaches, our evidence indicates that the BLA projections to the ventral hippocampus selectively influence the consolidation of the emotional, footshock-based component for contextual fear conditioning. In contrast, BLA projections to the medial entorhinal cortex modulate the consolidation of contextual and spatial memories, as assessed with both

contextual fear conditioning and Barnes maze-based tasks. Additionally, our findings indicate that stimulating the BLA afferents to the medial entorhinal cortex following training for a cued-response task in the Barnes maze impaired retention, in agreement with the hypothesis that spatial and cued-response learning use different neural systems that compete with one another. Moreover, across our studies, the findings suggest that only specific frequencies of stimulation are effective in enhancing memory. Whereas stimulating BLA afferents to the ventral hippocampus with bursts of 40 Hz stimulation enhances the consolidation of the footshock-based memories, stimulating BLA afferents to the medial entorhincal cortex is only effective at enhancing spatial memories and impairing cued-response memories when using bursts of 8 Hz stimulation.

Epigenetic regulation of the circadian gene Period1 in the hippocampus mediates age-related changes in memory and synaptic plasticity. Janine L. Kwapis[1], Yasaman Alaghband[1], Enikö A. Kramár[1], Alberto J. López[1], Annie Vogel Ciernia[2], André O. White[3], Guanhua Shu[1], Diane Rhee[1], Christina M. Michael[1], Emilie Montellier[1], Yu Liu[1], Christophe N. Magnan[1], Paolo Sassone-Corsi[1], Pierre Baldi[1], Dina P. Matheos[1], and Marcelo A. Wood[1]. 1University of California, Irvine, 2University of California, Davis, 3Mount Holyoke College. Aging is accompanied by impairments in both circadian rhythmicity and long-term memory. Although it is clear that memory is affected by circadian cycling, it is unknown whether age-related disruption of the circadian clock causes impaired hippocampal memory or whether these biological processes simply share a common mechanism that is altered with age. Here, we tested whether dysregulation of a key epigenetic mechanism, histone deacetylase 3 (HDAC3) in the aging hippocampus might contribute to impairments in long-term memory formation. HDAC3 typically represses gene expression by removing acetyl groups from histone tails and has previously been shown to be a key negative regulator of long-term memory formation. We found that deletion or disruption of HDAC3 in the dorsal hippocampus is sufficient to ameliorate age-related impairments in both long-term memory and synaptic plasticity. Further, RNA sequencing identified a subset of genes, including the circadian gene Per1, that is restricted in the aging hippocampus by HDAC3. Finally, we show that hippocampal *Per1* is critical for long-term memory formation and overexpression of *Per1* in the dorsal hippocampus can ameliorate age-related impairments in long-term memory formation. Together, our data suggest that HDAC3-mediated repression of *Per1* contributes to age-related impairments in long-term memory formation. More broadly, this age-related disruption of *Per1* might connect age-related impairments in both long-term memory and circadian rhythmicity, depending on the structure. Funding support: NIH MH101491, AG051807, & AG050787 to M.A.W. and NIH AG05696 & AG052303 to J.L.K.

The modulatory role of the endocannabinoid system on the consolidation and retrieval of memory for stressful experiences in rats. P. Campolongo. Dept. of Physiology and Pharmacology, Sapienza University of Rome, IRCCS Santa Lucia Foundation, 00143 Rome, Italy. Emerging evidence demonstrates that the level of stress associated to the environmental conditions plays a crucial role in modulating cannabinoid effects on emotional behaviors. I will discuss to what extent the level of stress, associated to the level of training-induced emotional arousal, might have implications on cannabinoid effects on memory consolidation and extinction. In particular, I will present data demonstrating that variations in the level of emotional arousal, associated to the experimental conditions, shape cannabinoid effects on memory functions. Funding acknowledgements: This work was supported by a grant from the Italian Ministry of Education MIUR (PRIN_2015SKN9YT_002) and Human Frontiers Science Program Young Investigator Grant n. RGY0077

Molecular mechanisms of memory reconsolidation and strengthening. Cristina M. Alberini, Center for Neural Science, New York University, New York. The ability to regulate the consolidation and strengthening of memories for threatening experiences is critical for mental health, and its dysregulation may lead to psychopathologies. Re-exposure to the context in which the threat was experienced can either increase or decrease fear response through distinct processes known, respectively, as reconsolidation or extinction. In recent studies we have employed context retrieval-dependent memory-enhancement in rats, and found that memory strengthens through activation of direct projections from dorsal hippocampus to prelimbic (PL) cortex and activation of critical PL molecular mechanisms. Among these mechanisms we found that while sustained PL brain-derived neurotrophic factor (BDNF) expression is required for memory consolidation, retrieval engages PL BDNF to regulate excitatory and inhibitory synaptic proteins neuroligin 1 and neuroligin 2, which

promote memory strengthening while inhibiting extinction. Thus, context retrieval-mediated fear-memory enhancement results from a concerted action of mechanisms that strengthen memory through reconsolidation while suppressing extinction. I will discuss concerted mechanisms of memory strengthening and extinction inhibition in memory consolidation, reconsolidation and strengthening. Funding: MH074736 and MH065635

1:30-3:30 **Symposium: Developmental and experiential factors influencing alcohol's effects on the brain.** Chair: Cheryl McCormick, Brock University.

Developmental ethanol and attention: Long-lasting dysregulation of attention performance and its underlying prefrontal circuitry. Emma L. Louth[1], Hanna D. Luctkar[1], Laura K. Spatafora[1], Charles D. Sutton[1], Christine L. Taylor[1], Craig D.C. Bailey[1]. 1University of Guelph. Chronic prenatal exposure to ethanol can lead to persistent teratogenic outcomes, which in humans fall under the umbrella description of fetal alcohol spectrum disorders (FASD). Although attention deficits comprise one of the most common cognitive impairments associated with FASD, the neuronal mechanisms underlying this outcome are not well understood. Our laboratory employed a mouse model of FASD to determine effects of developmental ethanol exposure on the structure and function of pyramidal neurons located within layer VI of the medial prefrontal cortex (mPFC). This neuronal population plays a critical role in normal attention. Mice were treated with binge-like ethanol or control during the second half of gestation and the first two weeks of postnatal life. We first tested for long-term effects during adulthood, where ethanol-treated mice exhibited impaired attention on the five-choice serial reaction time test. Here, ethanol-treated mice performed with decreased accuracy during initial training, and with an increased rate of omission during later stages of training that required the greatest attentional demand. Developmental ethanol treatment also imparted a long-term dysregulation to the physiology and morphology of mPFC layer VI neurons during adulthood, as neurons from ethanol-treated mice exhibited decreased intrinsic excitability, increased response to excitatory neurotransmission, and decreased size of apical dendrite trees. We then tested for near-term effects of developmental ethanol treatment on mPFC layer VI neurons during young postnatal life, shortly after treatment had ended, and were surprised to find ethanol effects that were absent (physiology) or mild (morphology) compared with those seen in adulthood. These combined findings suggest that developmental ethanol exposure may alter the developmental trajectory of mPFC layer VI neurons to dysregulate their mature function. Given the importance of this neuronal population for normal attention, this research suggests a novel mechanism by which developmental ethanol may impair this cognitive function.

Maternal care and sex differences in alcohol related behavior, anxiety and the brain. Nicole M. Cameron. Psychology Department, Binghamton University, Binghamton, N.Y. In humans, the co-occurrence of alcohol use disorders (AUD) and anxiety is relatively common. Our research investigates the effects of early life environment on AUD and anxiety, and the contribution of g-aminobutyric acid type-A (GABAA) and neurosteroids in both disorders. Long Evans rats demonstrate wide individual variations in maternal care level provided to pups during the first week of life. We have demonstrated sex differences in the effects of variations in maternal licking/grooming (LG) behavior in this species. In males, Low LG level is associated with increased sensitivity to the hypnotic effects of ethanol compared to High LG offspring. In females, Low LG level is associated with increased consumption and preference for 10% ethanol in a four-week two-bottle choice test and a three-day two-hour drinking test (in the dark), compared to High LG female offspring. Interestingly, natural variations in maternal care levels are also associated with differences in anxiety levels. Low LG female offspring showed greater levels of anxiety-like behavior, particularly at metestrus, in the elevated plus-maze and the elevated T-maze tests, while Low LG males showed more anxiety in the light/dark box test compared to High LG males. GABAA and neurosteroids have been implicated in AUD and anxiety. Maternal care programs neurosteroid and GABAA receptor function, as female offspring of Low LG mothers display dysregulation of GABAA/neurosteroids. Low LG female offspring have lower allopregnanolone (THP) levels within the dorsal hippocampus compared to High females. Furthermore, High LG females show correlations between hormone levels and GABAAR subunit expression, and this relationship is absent in Low LG females. Low LG adolescent males also express more GABAA a1 and d subunits in the cerebral cortex, but less in the cerebellum, compared to High LG males. Decreasing THP levels through treatment with finasteride (5a-reductase

inhibitor) removed the estrous-cycle dependent effect of maternal care on anxiety-like behavior. THP also modulates sensitivity to the hypnotic effects of ethanol. Our research suggest that early life environment modulates the co-occurrence of AUD and anxiety possibly through THP and GABAA receptor function, particularly in females. Furthermore, natural variations in LG in the rat is a novel animal model to study the mechanisms controlling the co-occurrence of AUD and anxiety. Funded by R21AA023072 and P50AA017823.

Social instability stress and social context distinctly influence the intake of ethanol and sucrose. Marcolin ML [1]; Hodges TE [2]; Baumbach JL [2]; McCormick CM [1,2] 1. Department of Biological Sciences, Brock University, ON, Canada 2. Department of Psychology, Brock University, ON, Canada. Introduction: Social instability stress in adolescent rats (SS; postnatal day 30-45, daily 1 hour isolation + new cage partner) alters behavioural responses to psychostimulants, but differences in voluntary consumption of natural and drug rewards is unknown. SS also increases anxiety and reduces aspects of social behaviour, although not the reward value of social interactions. Lastly, the social context may modify the intake of rewards. Here, we investigated whether SS rats differ from control (CTL) rats in ethanol (EtOH) or sucrose intake using different drinking approaches. Methods: Male no-stress (CTL) and SS rats were placed in an apparatus divided in half by a mesh, either alone or with an unfamiliar partner (social), and were randomly assigned to have access to 10% EtOH or 1% sucrose for 30 min (Social Drinking test). Then, for 5 consecutive days, pairs of familiar adolescent and adult male CTL and SS rats were placed on each side of the same apparatus for 1 hour, and were assigned to have access to a bottle of 10% EtOH or 1% sucrose and a bottle of water (Drinking Preference test). Finally, pairs of familiar adolescent and adult male CTL and SS rats were placed on a testing chamber and were allowed to drink from a feeder that only one rat could drink at a time; either 10% EtOH or 1% sucrose was available for 5 min during 5 consecutive days (Drinking Competition test). Results: Social Drinking: for EtOH groups, CTL rats had a longer latency to drink than SS rats, and alone rats had a longer latency than social rats. SS rats spent more time drinking EtOH than did CTL rats. Alone rats spent more time drinking than social rats. For Sucrose groups, there were no effects on latency to drink. Alone rats spent more time drinking than social rats. Drinking Preference: for EtOH groups, latency to drink increased over time, SS rats spent more time drinking EtOH than did CTL rats, and rats drunk more on the 1st compared to the 5th. For Sucrose groups, latency to drink decreased over time, and adolescent rats drunk more than adults on the 5th day. Drinking Competition: for EtOH groups, adolescent SS rats drunk more than CTL rats, while adults did not differ. For Sucrose groups, adolescent rats drunk more than adults, and SS rats drunk more than CTL rats. Conclusions: The increased EtOH consumption of SS rats compared with CTL may be associated with evidence of increased anxiety in SS rats and the anxiolytic properties of EtOH. SS and CTL rats do not differ in sucrose intake, which suggests no differences in sensitivity to the “hedonic” properties of sucrose. Adolescent rats drunk more sucrose than adults, which agrees with evidence that adolescents are more sensitive to “natural” rewards than older animals. The effect of peer presence on intake in alone and social conditions is in the opposite direction to previous reports with sweetened EtOH, which suggests that the effect of peers may depend on the degree of reward value of the substance.

Embryonic alcohol exposure in zebrafish: Modeling the milder and more prevalent form of Fetal Alcohol Spectrum Disorders. Robert Gerlai, Yohaan Fernandes, Diptendu Chatterjee, Christine Buske, Samantha Mahabir, Diane Seguin. Department of Psychology, University of Toronto Mississauga, Canada. Exposure of the human fetus to alcohol (ethanol or EtOH) leads to Fetal Alcohol Spectrum Disorders (FASD). Despite the clearly deleterious effects of this teratogen on the embryo, pregnant women continue to drink, and alcohol remains the leading preventable cause of mental underdevelopment and learning disability. FASD represent a large unmet medical need, and even diagnostic criteria such as biomarkers of the disease are unavailable. Animal models of FASD have started to explore mechanistic questions. The zebrafish has been proposed as a particularly useful species due to the fact that fertilization, and thus embryonic development, occurs outside of the mother, which allows precise manipulation of the timing and dose of alcohol exposure. Recently, a model of the mild, and most prevalent form of FASD, has been proposed with zebrafish. Here we review findings obtained with this model. Zebrafish embryos immersed for 2 hours in alcohol bath not exceeding 1% (vol/vol) concentration at the age of 24th hour post-fertilization, show no gross morphological or growth deficiencies, no alteration of motor function, visual perception, general motivation, or fear and anxiety responses. However, these fish

exposed during their embryonic development to alcohol exhibit a quasi-linear dose dependent reduction of behavioral responses to social stimuli (response to animated images of conspecifics, and distance among shoal mates in freely moving zebrafish groups) when tested at 6 months of age (adult stage), a permanent change detected even at 2 years of age (old). Correlating with this behavioral change is lack of social stimulus induced increase in dopamine and DOPAC levels (relative to total brain protein in the adult brain as quantified using HPLC of whole brain extract), as well as increased apoptotic cell death (Tunnel staining) and pro-apoptotic protein expression (Western Blot) in the developing embryo. The potential behavioral specificity of the alcohol induced social behavioral changes, and the possible underlying anatomical and neurobiological mechanisms are discussed.

1:30-3:30 **Symposium: Inflammation in psychiatric disorders: What we know and what is next.** Chair: Atsushi Kamiya, Johns Hopkins University School of Medicine. Co-Chair: Juliet Richetto, University of Zürich.

Sex differences in the immune response to stress. Georgia E. Hodes[1]. [1] School of Neuroscience, Virginia Polytechnic Institute and State University. Depression affects more than 300 million people worldwide. Pro-inflammatory cytokines and the activation of inflammatory pathways have been associated with depression. We will present data demonstrating a functional role for the peripheral immune system in the development of stress susceptibity in male animals. However, both depression and most autoimmune / inflammatory diseases have a higher incidence in females, presenting the possibility that immune system responses to stress may differ between males and females. To explore sex differences in the effects of stress or depression on the peripheral immune system we took an unbiased approach and examined cytokine concentrations in humans with MDD and mice exposed to either 6 or 28-day variable stress. Following 6 days of variable stress female but not male mice express a constellation of depression-associated behaviors. After 28 days of variable stress both sexes demonstrate stress susceptibility. We will discuss sex differences in the patterns of cytokine expression in animal models and their overlap with human MDD. Additional studies examine how stress vulnerability alters immune cell phenotype sex specifically and the implications of these sex differences to diagnosing and treating mood disorders. Funding: NARSAD Young investigator award from the Brain & Behavior Research foundation to GEH.

Microglial inflammation for exploring novel pharmacological intervention of stress-induced psychiatric disorders. Atsushi Kamiya [1]. [1] Johns Hopkins University School of Medicine. Many patients with stress-associated psychiatric disorders exhibit resistance to first-line interventions calling for novel interventions based on pathological mechanisms. Accumulating clinical evidence indicates the pathophysiological role of neuroinflammation in stress-induced psychiatric disorders including depression. Consistently, stress evokes CNS and peripheral inflammation in multiple rodent stress models, such as chronic social defeat stress (CSDS) model. CNS inflammation includes altered microglia function which may be a key pathological mechanism underlying stress-induced behavioral abnormalities. Although understanding microglial pathophysiology may open a new window for development of novel pharmacological interventions for stress-induced mental disorders, microglia-mediated molecular and circuit mechanisms underlying stress-induced behaviors remain elusive. In this session, I will present our recent finding utilizing novel microglia-associated pharmacological approach in CSDS model, which may contribute to treatment intervention for depression and related mental conditions.

Epigenetic and transgenerational effects of maternal immune activation. Juliet Richetto, Ulrike Weber-Stadlbauer, Urs Meyer. Institute for Veterinary Pharmacology and Toxicology, University of Zurich – Vetsuisse, Zurich, Switzerland. Prenatal exposure to infection is increasingly recognized to play an important etiological role in neuropsychiatric and neurological disorders with neurodevelopmental components, including schizophrenia, autism, bipolar disorder, and mental retardation. The adverse effects induced by prenatal infection may reflect an early entry into a deviant neurodevelopmental route, but the specificity of subsequent disease or symptoms is likely to be influenced by the genetic and environmental context in which the prenatal infectious process occurs. Modelling the human epidemiological association between prenatal infection and increased risk of neurodevelopmental disorders in animals has also greatly advanced our understanding of the underlying mechanisms. According to the prevailing view, cytokine-associated

inflammatory events, together with downstream pathophysiological effects such as oxidative stress and (temporary) macronutrient and micronutrient deficiency, seem critical in mediating the post-acute effects of maternal infection on the fetal system. Recent findings from our group have further implicated epigenetic processes as possible molecular mechanisms translating the negative effects of prenatal immune activation on the offspring. Indeed, using a well-established murine model of prenatal immune activation, we show that prenatal infection causes long-lasting genome-wide DNA methylation changes in the offspring that extend to different brain regions. These changes are paralleled by alterations in the expression pattern of multiple enzymes that regulate the epigenetic machinery. Interestingly, we also observed a transgenerational transmission of behavioral and epigenetic abnormalities without additional immune exposures, suggesting that prenatal infection and associated developmental neuroinflammation may have a pathological role in shaping neurodevelopmental disease risk across generations.

Adolescent cannabis exposure and astrocyte-specific genetic vulnerability synergistically activate inflammation signaling and affect cognition in adulthood. Mikhail V. Pletnikov, Yan Jouroukhin, Xiaolei Zhu, Alexey Shevelkin, Yuto Hasegawa, Alexis L. Norris, Bagrat Abazyan, Atsushi Saito, Jonathan Pevsner, Atsushi Kamiya. Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Adolescent cannabis use has been associated with long-term cognitive dysfunction attributed to action of the main cannabis ingredient, delta-9-tetrahydrocannabinol (Δ9-THC), on the cannabinoid receptor 1 (CNR1). However, variability in marihuana-associated cognitive impairment suggests a genetic vulnerability to adverse effects of cannabis. As both neurons and glial cells express CNR1, genetic vulnerability could influence Δ^9-THC-induced signaling in a cell type-specific manner. Here we use an animal model of inducible expression of dominant-negative Disrupted-In-Schizophrenia-1 (DN-DISC1) selectively in astrocytes to evaluate the molecular mechanisms whereby an astrocyte genetic vulnerability could synergistically interact with adolescent Δ^9-THC exposure to produce cognitive impairment in adulthood. Selective expression of DN-DISC1 in astrocytes and adolescent treatment with Δ^9-THC synergistically affected recognition memory in adult mice. Similar deficits in recognition memory were observed following knockdown of endogenous *Disc1* in hippocampal astrocytes in mice treated with Δ^9-THC during adolescence. At the molecular level, DN-DISC1 and Δ^9-THC synergistically activated the NF-kB-PTGS2 (formerly called COX2) pathway in astrocytes and decreased immunoreactivity of parvalbumin-positive pre-synaptic boutons around pyramidal neurons of the CA3 area of the hippocampus. The cognitive abnormalities were prevented in DN-DISC1 mice exposed to Δ9-THC by simultaneous treatment with the PTGS2 inhibitor, NS389. Our data demonstrate that genetic mutations within astrocytes can exaggerate cognitive impairments produced by adolescent Δ^9-THC exposure and suggest possible targets for preventing adverse effects of cannabis.

4:00-6:00 **Symposium: The end of chronic stress, or is it?** Chair: Cheryl Conrad, Arizona State University.

Animal model of anorexia nervosa: Behavioral, neurochemical and anatomical changes that persist beyond weight restoration. Chiye Aoki, Evelyn Y-W Chen, Ang. D. Sherpa, Tara G. Chowdhury, Gauri S. Wable, Adrienne N. Santiago. New York University. Aoki will describe the cellular basis of executive control over maladaptive impulsivity that emerges from mid- to late-adolescence, based on insights gained from studying an animal model of activity-based anorexia. Aoki will discuss the putative role of three molecules and two neural pathways within the still-developing dorsal hippocampus and prefrontal cortex in the emergence of this behavior during adolescence. Aoki will first show how voluntary exercise for 8 days, food restriction for 4 days and the combination of the two during mid-adolescence exert strong, lasting influence on the complexity of dendritic branches of hippocampal pyramidal neurons. The same environmental treatments also improve spatial cognition, as is indicated by analysis of active place avoidance tests conducted 7 days after these environmental manipulations. Aoki will then describe the phenomenon of activity-based anorexia, whereby wheel-acclimated adolescent mice exhibit rapid increases in wheel running within 6 hours of food deprivation and continues to run even during the hours of food availability. Although running is adaptive to starving animals in the wild, as it promotes foraging, this behavior is maladaptive for cage-reared animals: animals can perish, unless the wheel is removed from the environment. Curiously, the number of animals that become maladaptive excessive runners drops from 80% at mid-

adolescence to 50% at late-adolescence and to nearly 0% in adulthood. This could be because of the maturation of pathways underlying executive function that suppresses the innate impulsive behavior of excessive running. Aoki will then present outcomes from EM:behavior correlational analyses that provide clues about the cells and molecules that may promote the executive function. The molecules identified so far are the (1) non-synaptic a4bd-GABAA receptors that mediate shunting inhibition and (2) glutamate transporter, GLT-1, responsible for up-take of extrasynaptic glutamate. Conversely, individuals exhibiting the greatest weight loss express the highest levels of (3) NR2B-subunits of NMDARs, suggesting an interplay among the three molecules in setting the excitability-to-inhibition ratio of pyramidal neurons within brains of animals deciding to eat or to run. Further analysis of GABAergic synapses in the prefrontal cortex and hippocampus suggests that plasticity of these synapses also contribute to suppression of the maladaptive behavior of excessive running.

Cortical integration of behavioral and physiological stress responses. Tyler Wallace[1], Derek Schaeuble[1], Sebastian Pace[1], James P. Herman[2], Brent Myers[1] [1]Biomedical Sciences, Colorado State University, Fort Collins, CO [2]Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH. Stress, defined as a real or perceived threat to homeostasis or well-being, has a considerable role in the pathogenesis of mood and anxiety disorders. Moreover, prolonged stress and mood disorders are significant risk factors for numerous cardiometabolic conditions that further burden health-related quality of life. The neurobiological mechanisms of stress-related health detriments remain elusive; however, we have identified a specific population of chronic stress-activated glutamate neurons in infralimbic cortex that integrate behavioral and physiological responses to stress. Large-scale quantitative circuit mapping in rats identified a network of projections from these cells to numerous behavioral and homeostatic regulatory regions. Furthermore, lentiviral-mediated knockdown of vesicular glutamate transporter 1 (vGluT1) in infralimbic cortex was employed to reduce presynaptic vesicular glutamate packaging and excitatory outflow from infralimbic cortex in rats undergoing chronic variable stress. This produced a marked divergence of behavioral and physiological stress responding. In terms of behavior, rats with vGluT1 knockdown were protected from the effects of chronic stress on avoidance, depression-like, and anxiety-related behaviors. In contrast, rats experiencing chronic stress with reduced infralimbic outflow exhibited enhanced physiological reactivity to chronic stress. In fact, vGluT1 knockdown and chronic stress interacted to increase basal and stress-induced corticosteroid secretion, enhance heart rate reactivity to stress, elevate chronic blood pressure, and induce vascular endothelial dysfunction. In order to test the hypothesis that infralimbic neurons coordinate the behavioral and physiological aspects of stress responding, we utilized an optogenetic approach to stimulate infralimbic glutamate neurons and investigate mood-related behaviors as well as physiological stress reactivity. These studies uncovered a role for infralimbic cortex in the concordance of behavior and physiological status. Specifically, optogenetic activation of infralimbic glutamate neurons induced place preference and increased social motivation. This was coupled with reduced autonomic and endocrine stress reactivity. Collectively, these studies highlight infralimbic cortical neurons as a critical component of the neural networks mediating stress chronicity and the adaptive integration of behavioral strategy with physiological status. Supported by NIH grant K99/R00 HL122454 to B. Myers

Hippocampal mechanisms involved in the improvement from cognitive deficits following the end of chronic stress. Cheryl D. Conrad[1] and J. Bryce Ortiz[1,2], [1]Arizona State University, [2]Currently at the University of Arizona. Chronic stress results in functional and structural changes to many brain regions, especially the hippocampus. A common finding following a period of chronic stress is deficits in hippocampal mediated cognition with a concomitant decrease in the dendritic complexity of pyramidal neurons in the hippocampal CA3 region. Many years of research have provided insights into the mechanisms by which chronic stress impairs hippocampal-mediated cognition and the corresponding reduction of hippocampal CA3 apical dendritic complexity. However, an understudied phenomenon is the process by which these mechanisms can improve following the end of stress. Indeed, when chronic stress ends and time passes, which we refer to as a “post-stress rest period,” hippocampal-mediated spatial memory deficits begin to improve and CA3 apical dendritic arbors increase in complexity. Here we describe a series of experiments showing that brain derived neurotrophic factor (BDNF) and its TrkB receptor are critical for these post-stress improvements. We found that by decreasing the expression of hippocampal BDNF, both spatial memory improvements and the increase in hippocampal

dendritic complexity were prevented following the post-stress rest period. We then followed up on this study to show that systemic administration of a TrkB antagonist, during the post-stress rest period only, also prevented the improvements in spatial ability and dendritic complexity following the end of stress. These studies together show that BDNF and its TrkB receptor are required in the hippocampus and during the post-stress rest period for spatial memory and hippocampal dendritic complexity improvements to occur following the rest period. Next, we addressed the involvement of the hippocampal GABAergic system, and how changes to this system play a role in the post-stress rest period. While chronic stress or a post-stress rest period had no impact on the total number of hippocampal GABAergic interneurons, various subtypes of GABAergic interneurons were altered in response to the stressor manipulations. Collectively, these studies elucidate some mechanisms that are important for the post-stress plasticity that allows for improvements from stress-induced deficits in hippocampal mediated cognition. Untangling the mechanisms that allow for this post-stress plasticity is a critical next step in understanding how to promote resilience in the face of stressors.

Sex differences in risk and resilience: Recovery of stress-induced dysfunction of prefrontal cortex in male and female rats. Kelly M. Moench and Cara L. Wellman. Indiana University. Department of Psychological and Brain Sciences, Program in Neuroscience, and Center for the Integrative Study of Animal Behavior, Indiana University, Bloomington, IN, USA. Prefrontal cortex is critical for executive function and emotion regulation, regulates stress-related behaviors, and is implicated in many stress-influenced and sex-dependent psychological disorders. Women are at increased risk for many of these stress-related disorders, yet the mechanisms underlying this vulnerability are currently unknown. In animal models focusing on the immediate effects of chronic stress, deleterious effects on the structure and function of prefrontal cortex in males have been extensively documented. Interestingly, females do not show these deleterious effects immediately post-stress. Recent data from our lab demonstrate dendritic remodeling in prefrontal cortex of males but not females in the days following the cessation of chronic stress. Further, we showed that chronically stressed male and female rats show differential responses to a novel acute stressor in the days following chronic stress: Exposure to heterotypic acute stress 7days after the cessation of chronic stress increases activation of neurons in the periventricular nucleus of the hypothalamus inn female but not male rats. These differences are accompanied by sex-dependent changes in BDNF and NPY expression in, and activation of, prefrontal cortex. This increased responsivity to a subsequent stressor may have profound implications for the effects of stress on prefrontally mediated behaviors. To test this hypothesis, we assessed whether prior exposure to chronic stress influences the effect of acute stress on behavioral flexibility using an attentional set-shifting task in male and female rats. Immediately following chronic stress, males had a deficit in behavioral flexibility specific to extradimensional shifting. This deficit was ameliorated following a 7-day post-stress rest period. Further, exposure to a heterotypic acute stressor after the rest period did not impair EDS in males. In contrast, females showed no deficit in set-shifting following chronic stress. Interestingly, deficits in EDS emerged in chronically stressed female rats after exposure to a heterotypic acute stressor 7 days post-chronic stress. Together, these data suggest that stress-related plasticity in prefrontal cortex of males following stress may confer resilience to subsequent novel stressors—a resilience that is absent in females, potentially an important clue to the increased risk for stress-related psychopathology in women. This work was supported by the Indiana Clinical and Translational Sciences Institute, funded in part by Grant Number UL1TR001108 from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award; and National Institute of Mental Health Award Number T32MH103213.

4:00-5:45 **Oral Session 1:** Chair: Michael Bowen, University of Sydney

High precision and transient stimulation from advanced automated laser tracking and optogenetic manipulation system (a-ALTOMS) manipulation neuronal circuit during operant restraining memory. Po-Yen Hsiao[1], Ming-Chin Wu[1], Yen-Yin Lin[1] and Ann-Shyn Chiang[1,2,3] 1 Brain Research Center, National Tsing Hua University, Hsinchu 30013, Taiwan. 2 Institute of Biotechnology, National Tsing Hua University, Hsinchu 30013, Taiwan. 3 Kavli Institute for Brain and Mind, University of California, San Diego, La Jolla, CA 92093-0526, USA. A comprehensive understanding of what relationship between behavioral diversity and neural circuits is important question in neuroscience. However, it was still challenging task to

address what function of interneuron activation in freely-moving *Drosophila.* In this study, we developed an advanced automated laser tracking and optogenetic manipulation system (a-ALTOMS), a system that provided a useful single platform, which enables neural manipulation simultaneously on different body part and a zoom view window of freely-moving larval and adult fly. To address precision and transient laser stimulation from a-ALTOMS manipulating, we selected *12862-Gal4* to drive both ChR2 and NpHR expression in the giant fiber neurons. These results suggest that laser irradiation effectively triggers ChR2 and NpHR and that high precision and transient manipulation giant fiber neuron within different body part during online tracking, and provides an effective method for determining the information processing from interneuron. Taking the advantage of a-ALTOMS, we created a operant restraining memory assay in unrestrained flies. Applying 1064-nm IR laser irradiation as an aversive unconditioned stimulus, a courting male could quickly learn to stay away from a freely moving virgin female. By behavioural screening, operant restraining memory requires olfactory system (*or47b* neurons)、dopamine neurons (MB-MV1 neurons) and pain neuronal circuits. In addition, optogenetic manipulation of neuronal activities with NpHR inhibition revealed an ensemble of brain neurons orchestrating this distance-restraining social memory. These results show that γ lobe of MB were involved in acquisition of the restraining learning and α'/β' lobe of MB were involved in retrieval of the restraining learning. Thus, a-ALTOMS offers opportunities to systematically map operanr restraining circuits that orchestrate specific *Drosophila* behaviors.

Alleviating cognitive impairments in Mild Neurocognitive Disorder using transcranial infrared laser stimulation. Courtney Alexander, M.S.[1]; Celeste L. Saucedo[1]; Janelle T. Foret[2]; Douglas W. Barrett[1]; Andreana P. Haley[2]; F. Gonzalez-Lima[1] 1University of Texas at Austin, Behavioral Neuroscience 2University of Texas at Austin, Clinical Psychology. Transcranial infrared laser stimulation (TILS) of the prefrontal cortex is a novel intervention that can potentially enhance human brain functions and protect against cognitive and affective deficits. The primary mechanism of action of TILS is the delivery of photons to brain cells, upregulating the enzymatic activity of cytochrome oxidase in vivo, enhancing the brain's ability to utilize oxygen and increasing its metabolic energy capacity. In this ongoing study, cognitive and affective impairment was assessed using: Positive and Negative Affect Schedule (PANAS-X), Montreal Cognitive Assessment (MoCA) and the Frontal Assessment Battery (FAB). Test batteries were administered before TILS (baseline) and one week after four weekly sessions of TILS (post-treatment) to the right prefrontal cortex. Participants were separated into three groups based on MoCA scores or presence of neurological condition: healthy controls (n=6, MoCA score ≥ 26), cognitive impairment symptoms (n=5, MoCA < 26), and other neurological condition (n=5, TBI, stroke, Parkinson's). Preliminary data reported here are changes over 5% in participants given active TILS. Healthy controls showed an 8% increase in FAB scores, but no further increase in MoCA scores that were close to ceiling. However, the cognitive impairment group showed +7% improvements in both MoCA and FAB cognitive measures across the five-week period. Patients with neurological conditions showed small changes in cognitive scores; however, they had a 10% increase in positive affect. It appears subjects with cognitive impairment benefited the most from prefrontal TILS in both MoCA and FAB cognitive measures, while those with neurological conditions benefited primarily in affect. This study is on-going. Research is supported by the Oskar Fischer Fund.

Infrared laser stimulation enhances sustained attention and working memory in mild neurocognitive impairment. Celeste L. Saucedo, Courtney Alexander, Douglas W. Barrett, & F. Gonzalez-Lima. 1University of Texas at Austin. We investigated for the first time the enhancing effects of prefrontal infrared laser stimulation on sustained attention and working memory in adults experiencing symptoms of mild neurocognitive impairment. Transcranial infrared laser stimulation involves non-invasive delivery of infrared photons to the cerebral cortex to enhance neurobiological functions. We have previously shown that, when targeted at the prefrontal cortex, a single session of infrared laser stimulation can improve executive function, rule-based category learning, sustained attention and working memory in young healthy adults. In this ongoing project, participants (ages 30-73, n=11) with symptoms of mild neurocognitive impairment completed a psychomotor vigilance task (PVT) and two delayed match-to-sample tasks (DMS), one easier and another more difficult DMS task (i.e., 4x4 and 6x6 matrix), before and after four or six weekly laser sessions. Preliminary findings revealed improved sustained attention as measured by PVT reaction time in 9 participants. Working memory as measured by number of correct responses improved in 7 participants on the easy task (DMS 4x4) and in 7 participants on the difficult

task (DMS 6x6). Additionally, 4 of the 7 participants that improved on DMS 4x4 and 5 of the 7 that improved on DMS 6x6 also showed improvement in memory retrieval times. This novel, non-invasive technique has been shown to up-regulate the amount of the respiratory enzyme cytochrome oxidase (CCO), the major intracellular acceptor of photons from near-infrared light in the brain. This upregulation of CCO enhances cerebral oxygenation and energy production, which facilitates cognitive performance. Applications of transcranial infrared laser stimulation in humans *in vivo* are novel and promising for wide-ranging experimental and clinical applications, including prevention of cognitive decline.

Orphan receptor GPR158 controls stress-induced depression. Laurie P. Sutton, Cesare Orlandi, Kirill A. Martemyanov. The Scripps Research Institute, Department of Neuroscience, Jupiter, FL. Stress can be a motivational force for decisive action and coping with novel environments and yet, exposure to chronic stress can develop into maladaptive responses including clinical depression and anxiety disorders. However, the molecular mechanisms underlying stress-responsive behaviors are not fully understood. Here, we screened orphan receptors for potential stress-regulated gene in the medial prefrontal cortex (mPFC). Orphan receptor are G-protein-coupled receptors (GPCRs) whose cognate ligands are unknown, leaving their physiological function in doubt. We identified the orphan receptor GPR158, the most abundant GPCR in the PFC, as a molecular determinant in mood regulation and stress resiliency. We found that GPR158 levels are increased in the postmortem dlPFC of human subjects with major depressive disorder (MDD) relative to matched controls. Exposure to chronic stress in mice also increased GPR158 in the PFC in a glucocorticoid-dependent manner. To assess the overall behavioral consistency among tests assessing anxiety-like and depressant-like behaviors (marble burying, elevated plus maze, tail suspension and force swim tests) and to reduce bias introduced by individual tests we calculated an aggregate 'emotionality score' by meta-analysis of all behavioral data by z-scoring methodology. Mice with a viral overexpression of GPR158 in the mPFC had a higher emotionality score, indicating that elevated GPR158 is sufficient to induce depressive-like behaviors. In contrast, mutant mice with a deletion of the gene encoding GPR158 displayed a prominent antidepressant-like phenotype and exhibited a resiliency to chronic stress. These knockout mice also showed an increase in spine density in the glutamatergic neurons in the mPFC. Taken together, our findings identify a novel mechanism for mood regulation and introduce a potential pharmacological target for managing depression.

Interrelationship between synaptic connectivity and neurocognitive impairments (NCI) in the HIV-1 transgenic rat. Kristen A. McLaurin, Hailong Li Rosemarie M. Booze, Charles F. Mactutus, University of South Carolina, Columbia, SC, 29208. HIV-1 associated neurocognitive disorders (HAND) remain prevalent in the post-cART era, afflicting between 40-70% of HIV-1 seropositive individuals. Using the HIV-1 transgenic (Tg) rat, which resembles HIV-1+ individuals on cART, synaptopathy, a potential neural mechanism was examined. First, post-mortem synaptopathy was assessed in layers II-III pyramidal neurons of the medial prefrontal cortex at approximately 20 months of age (HIV-1 Tg: N=19 litters: Male: n=28, Female: n=27; control N=16 litters: Male: n=26, Female: n=20). HIV-1 Tg animals, independent of biological sex and spine type (i.e., thin, stubby, mushroom), displayed an increased relative frequency of spines on lower order branches; observations that are consistent with an alteration in synaptic connectivity. Morphologically, HIV-1 Tg animals exhibited a selective population shift in dendritic spine backbone length, volume, and head diameter, dependent upon biological sex, relative to control animals. Male HIV-1 Tg animals exhibited a population shift towards shorter dendritic spines with increased head diameter and increased volume relative to male control animals. In contrast, female HIV-1 Tg animals displayed a population shift towards longer dendritic spines with decreased head diameter relative to female control animals; no significant alterations in dendritic spine volume were revealed in female HIV-1 Tg animals relative to female control animals. Second, the relationship between post-mortem synaptopathy and NCI at an advanced age (i.e., 18 months) was assessed. In male animals, HIV-1 Tg and control animals displayed a differential brain behavior relationship between branch order and the number of misses at 10 msec in a signal detection task. Female control animals, however, displayed a brain/behavior relationship between branch order and the number of hits at 1000 msec in a reversal task; a brain/behavior relationship not observed in female HIV-1 Tg animals. Thus, alterations in synaptic connectivity, independent of changes in dendritic spine morphology, may mechanistically underlie NCI in the HIV-1 Tg rat, providing key targets for functional cure strategies. Funded by: NIH DA013137, HD043680, MH106392, NS100624.

Restoration of synaptic integrity and function following HIV-1 induced damage. Rosemarie M. Booze, Kristen McLaurin, Charles F. Mactutus. University of South Carolina. The challenge of HIV-1 cures may require specific strategies for improvement of cognitive dysfunction. In particular, HIV-1 is associated with dendritic simplification and synaptic loss. Recovery from HIV-1 induced synaptodendritic damage may be key in the functional effectiveness of CNS gene excision cure strategies. We have been investigating compounds/treatments which may promote synaptic neurorestoration following HI-1. We first examined the integrity of the dendritic network after exposure to HIV-1 Tat by labeling filamentous acting (F-actin)-rich structures (puncta/spines) in primary neuronal cultures. After 24 h of treatment, HIV-1 Tat produced a significant reduction of F-actin-labeled dendritic puncta/spines as well as loss of dendrites. However, 6 days after HIV-1 Tat phytoestrogens enhanced synaptic recovery. These results suggest that specific neurosteroidal compounds, such as phytoestrogens, may not only attenuate acute synaptodendritic injury in HIV-1, but may also promote recovery from HIV-1-induced synaptodendritic damage. We found synaptic restoration was specifically mediated by estrogen receptors (ER). In further studies, synaptic integrity was assessed following exposure to low concentrations of the HIV-1 Tat and the phytoestrogen, S-equol. HIV-1 induced synaptic reduction was prevented by S-equol in an estrogen receptor beta subtype specific manner. In vivo experiments using HIV-1 transgenic rats to study functional recovery from deficits in executive function produced by HIV-1 proteins, found that oral S-equol had beneficial effects and enhanced the structural integrity of dendritic spines/synapses. These results suggest that certain steroidal compounds may promote functional neurorestoration from HIV-1-induced synaptopathy. In sum, targeted therapeutic interventions may enhance synaptic recovery, thereby promoting functional neurorestoration following HIV-1 gene excision. Supported by HD043680, MH106392, DA013137, NS100624.

Modeling neuroHIV progression in the post-cART era. Charles F. Mactutus, Kristen A. McLaurin, and Rosemarie M. Booze, University of South Carolina, Columbia SC 29208. Although 73% of HIV-1 seropositive individuals will be 50 years or older by 2030 (Smit et al., 2015), no model has been established to evaluate the progression of HIV-1 associated neurocognitive impairment (NCI). Progression of sustained attention was examined in the HIV-1 transgenic (Tg) rat, to address this knowledge gap, using a longitudinal experimental design; the factor of biological sex was integral to the experimental design. The guiding hypothesis was that HIV-1 Tg animals would exhibit significant alterations in the progression of neurocognitive impairment; deficits that may be moderated by biological sex. At approximately two months of age, male and female HIV-1 Tg (N=20 litters; male: n=37, female: n=33) and control (N=17 litters; male: n=34, female: n=33) animals were trained in a signal detection operant task with varying signal durations (1000-100 msec) until meeting criteria (70% accuracy for 5 consecutive or 7 non-consecutive days). Animals were retested every 60 days across their functional lifespan. At 18 months of age, animals were challenged for five consecutive days with shorter signal durations (1000-10 msec), followed by a reversal task, to assess the animals' ability to learn a new task at an advanced age. Evaluation of sensory and motor function every 60 days failed to reveal any significant confound for neurocognitive assessments. From the earliest assessment, HIV-1 Tg rats exhibited a deficit in task acquisition which progressed across retests. In contrast, a robust sex difference dissipated across retests. Despite the "savings" afforded by repeated testing, HIV-1 Tg animals displayed a relative impairment in the detection of shorter signal durations. The more challenging signal detection task at 18 months of age revealed a greater relative impairment in HIV-1 Tg rats than when they were first trained as young adults. The reversal task, which taps flexibility and inhibition, revealed marked impairment in the detection of shorter signal durations in the HIV-1 Tg rat. The progression of NCI with age in the HIV-1 Tg rat, in the absence of significant sensory deficits or motor impairment, affords an essential and critical model system for functional cure strategies. Funding: MH074736 and MH065635

4:00-6:00 **Symposium: Cingulate cortex: The who, what and how of cognitive control.** Chair: Jill McGaughy, University of New Hampshire Durham, NH USA. Co-Chair: Emmanuel Procyk, Stem Cell and Brain Research Institute, University of Lyon, Lyon, France.

Decoding predictions about the future in anterior cingulate cortex ensembles. James M. Hyman. University of Nevada Las Vegas, Department of Psychology, Las Vegas, NV. The ability to behave flexibly in a changing world is thought to be a

strong indicator of intelligence across the animal kingdom. To be successful an organism must keep track of their behavioral outputs and monitor the outcomes generated by their actions. Over the course of learning a certain outcome will be expected for a certain behavior and if this pattern continues then everything will be fine. But, when the unexpected happens then the organism needs to be flexible in their behavior to obtain the desired outcome. This process is called cognitive control and the best characterized neural instantiation of this are called neural prediction errors (PE; i.e. neural signals that differentiate whether an outcome was expected or not). My lab has recently developed a novel rodent task that closely mirrors a task used to study neural PEs in humans. We concentrate on the anterior cingulate cortex (ACC), an area known to be important for behavioral flexibility and cognitive control. Using this task, we have found two distinct neural PE signals in the rodent ACC. First, we found that ACC local field potentials strongly differentiated between expected and unexpected outcomes. These signals also signaled whether an outcome was better or worse than expected, or a signed PE. Next, we found that behaviorally linked ACC units produced another PE signal via changes in ensemble activity states. We discovered that if rewarded outcomes were more likely, then these ensembles would 'predict' a reward outcome on the next trial. The prediction would appear in the form of reward outcome activity states that arose during action initiation or well before the outcome was encountered. If on that trial a reward was given, then this same state would persist; however, if no reward was given on that trial, the ensemble would immediately switch to a no-reward outcome state. This rapid state transition from the expected to the actual outcome was greater when the unexpected outcome occurred, thus making this a form of neural PE. During trials where a non-rewarded outcome was more likely, the opposite occurred. Together, these two results show that ACC neural codes contain information that predicts the likely outcome of an action and tracks whether that prediction was correct or not. These findings reveal the cognitive control mechanisms employed by the ACC that enable behavioral flexibility.

Anterior Cingulate Cortex and Cognitive Control in the rat: Insights from chemo-architecture. Jill A. McGaughy[1], Lori A. Newman[2]. 1.University of New Hampshire, 2. Vassar College. The anterior cingulate cortex (ACC) has been hypothesized to underlie aspects of cognitive control. In rats, the interpretation of lesion and pharmacological studies of the ACC are complicated by effects produced by diffusion to the nearby prelimbic cortex (PL). Few data exist to dissociate clearly the function of the ACC from the PL in rats. Moreover, there are several neuromodulatory systems associated with cognitive control including, but not limited to, norepinephrine (NE) and acetylcholine (ACH). While prior data have shown distinct contributions of NE and ACH to the function of the PL in rat, few studies have dissociated the function of these two neuromodulators in the ACC. Here we will examine the effects of non-specific lesions of the ACC on tests of attentional set-shifting, distractibility and conflict monitoring. We will then provide novel data of the effects of specific noradrenergic or cholinergic lesions to the ACC on attentional set-formation, set-shifting and susceptibility to salient distractors. The results of these studies will highlight chemoarchitectural differences between the ACC and PL with respect to ACH and NE. Finally, these data will be synthesized with other data on the role of the ACC in primates to identify critical gaps in translational neuroscience that may impede our understanding of the function of these regions. Because dysfunction in this region has been linked to many neuropsychiatric disorders including major depression, schizophrenia, addiction, attention deficit disorder and autism the implications of these studies are expected to be widespread.

Combined role of primate midcingulate cortex in feedback processing and exploratory decisions. Emmanuel Procyk, Céline Amiez, Charles R.E. Wilson, Frederic Stoll. Univ Lyon, Université Claude Bernard Lyon, Institut National de la Santé Et de la Recherche Médicale, Stem Cell and Brain Research Institute U1208, Bron, France. The midcingulate cortex appears to be one important anatomo-functional hub in the frontal cortex. It has connections with limbic, dorsal cognitive and primary sensorimotor structures. Its precise function is highly debated but most would agree that it has an important role in adaptive cognition, and in mechanisms allowing to learn to adjust decisions. Here we will show that such role can clearly be observed in adaptive behavioral tasks requiring exploration for rewards in both humans and nonhuman primates with a very clear homology. Single unit activity in monkeys' midcingulate cortex reveals the dynamics of exploratory decisions but also a functional overlap between feedback (outcome) processing and exploratory decisions, feedback that in principles is used to regulate decision making. Preliminary pharmacological data show however a very

subtle causal role of the MCC in regulating the rate of exploratory decision but not reactive post-feedback adaptation. Altogether, these data provide novel evidence on the implication of MCC in adapting decision making.

Comparison of the organisation of the ACC using rs-fMRI in humans and animal models. Sallet Jerome[1,2,] Lopez-Persem Alizee [1,2,] Rushworth Matthew[1,2], Mars Rogier [1,3]1. Wellcome Neuroimaging Centre, University of Oxford, UK. 2. Department of Experimental Psychology, University of Oxford, UK. 3. Nuffield Department of Clinical Neurosciences, University of Oxford, UK. The anterior cingulate cortex (ACC) has been associated with multiple functions in reward-guided decision and social cognition. However the ACC is not a homogenous brain region supporting a single overarching function. Defining the function(s) of a brain area requires first an understanding of its anatomical organization. Its connections with other brain areas are indeed constraining the function it can support. Moreover there is a huge interindividual variability of the morphological sulcal patterns. Sulcal patterns could vary either in term of presence/absence but also in terms of relative position to one from another. Functional neuroimaging studies are classically based on statistical inferences based on the average brain activity of a group of subjects and they ignore those differences. However, taking into account the variability in sulcal patterns has proven to be essential to guide the interpretation of neuroimaging studies. I will first present results regarding the organization of the ACC, with a specific focus on the most anterior subdivision, but also on the impact of the inter-individual variability of the sulcal pattern on its organization. Secondly I will use neuroimaging tools to identify the intrinsic organization of the regions based on functional connectivity pattern analysis in animal models used to investigate neuroscience of decision-making and social cognition. Those results will be interpreted in light of their counterparts in the human brain.

6:30-8:30 Poster Session 1:

1. Hippocampal Cav1.2 channels mediate extinction of cocaine-associated memories via dopamine D1R activation. Caitlin E. Burgdorf[1,2], Delaney Fischer[1], Charlotte C. Bavley[1,2], Arlene Martinez-Rivera[1], Jonathan Hackett[1], Anjali M. Rajadhyaksha[1,2]. 1 Pediatric Neurology, Pediatrics, 2 Feil Family Brain and Mind and Research Institute, 3 Department of Psychiatry, 4 Department of Pharmacology, 5 Sackler Institute for Developmental Psychobiology Weill Cornell Medicine, New York, NY 10065. Cocaine addiction is characterized by persistent drug seeking that is often initiated following exposure to contextual cues associated with the rewarding effects of the drug. Extinction of these contextual cocaine-associated memories may act as a means to decrease relapse behavior, although the molecular mechanism underlying the learning of this new context-associated extinction memory is not well understood. Through the use of chemogenetic manipulations, we have found that dopamine D1R-expressing cells in the dorsal hippocampus are required for extinction of cocaine contextual memories, as measured by cocaine conditioned place preference. In an effort to identify downstream D1R signaling pathways recruited for extinction, we have found that extinction of cocaine CPP results in phosphorylation of the L type Ca^{2+} channel $Ca_v1.2$ at S1928, a site phosphorylated by PKA activated downstream of D1R. We also find that conditional knockout of Cav1.2 in D1R expressing cells attenuates extinction and is required in the dorsal hippocampus for cocaine CPP extinction. As $Ca_v1.2$ is associated with long term changes in activity-dependent gene expression, we performed molecular studies to investigate extinction-induced changes in $Ca_v1.2$-regulated transcription factors CREB and NFATc3 within the hippocampal nucleus. We found that extinction increased CREB, P-CREB and NFATc3 levels that were attenuated in extinction-resistant $D1^{Cre}$, $Ca_v1.2$ KO mice. Future studies aim to investigate the role of $Ca_v1.2$ in gene expression changes within D1R-containing cells of the dorsal hippocampus during extinction of cocaine-associated memories, in addition to mapping the dopaminergic inputs into the dorsal hippocampus. In sum, these studies suggest that $Ca_v1.2$ within D1R-expressing cells of the dorsal hippocampus may mediate extinction of contextual cocaine-associated memories and represent a pathway that can be explored for future pharmacotherapies towards treatment of cocaine addiction.

2. Acute administration of estradiol or progesterone during conditioning leads to divergent effects on the acquisition and expression of cocaine CPP. Saurabh S. Kokane & Linda I. Perrotti. The University of Texas at Arlington. Cue-sensitization is an important aspect of drug addiction. Exposure to drug-associated cues leads to drug craving and subjective feelings associated with drug consumption. Previous studies report that in women, specifically, this process is mediated and potentiated by estradiol. However, the direct effects of acute elevations in ovarian hormones on the development of associations to drug-paired environmental cues are virtually unknown. Previous data from our lab, demonstrated that a single acute treatment of estradiol given to ovariectomized (OVX) rats 30 minutes prior to a test for cocaine-conditioned place preference (cocaine-CPP) increased the threshold conditioning dose necessary to express preference for cocaine-paired stimuli. The goal of the present study was to understand the influence of acute elevations in levels of estradiol (EB) and progesterone (P4) during conditioning on the development of cocaine-environment associations. Thus, OVX female rats were subjected to a cocaine-CPP paradigm over five days; we used a 3/3 (AM/PM) conditioning procedure with intraperitoneal injections of 10mg/kg of cocaine hydrochloride (Sigma) or saline immediately before confinement in one compartment for 30 minutes. In order to systematically compare the effects of EB and P4 during the acquisition (conditioning stage) of cocaine-CPP, rats were treated with either EB (5 µg; s.c.), P4 (500 µg; s.c.), or peanut oil (PO; equal volume; s.c.) 30 minutes prior to the start of each daily conditioning session. Expression of cocaine-CPP was assessed 24h following the last conditioning session when animals were allowed free access to all compartments for a 15-minute posttest session. Results demonstrate that using a threshold conditioning dose of cocaine (10 mg/kg), only animals treated with EB during the conditioning stage of the CPP paradigm developed significant preference for cocaine-paired compartment whereas those that were treated with P4 or PO failed to express cocaine-CPP. Preliminary analysis for BDNF in reward related regions suggests that hormone replacement increased BDNF protein expression in the dorsal striatum, but not ventral, striatal

regions. Further analyses of these data is ongoing. Our results confirm and extend a growing body of evidence showing that estrogen and progesterone have divergent influences on activities within the reward system that govern drug-directed behaviors. Funding support: NIH/NIDA R15DA040809 (LIP).

3. Effects of ICI 182,780 on preference for cocaine in male rats. Jacqueline A. Quigley, Lahin K. Lalani, Benjamin G. Lipkin, & Jill B. Becker. University of Michigan. There are sex differences in motivation for cocaine and cocaine-taking behavior in rodents. Susceptibility to addiction and addiction-like behaviors in females are modulated by estradiol. Research from the Becker laboratory has shown that estradiol enhances the cocaine-induced increase in dopamine in the dorsal striatum of female rats, but not male rats. This enhanced increase in dorsal striatum dopamine is thought to mediate the increased susceptibility of females to addiction and drug abuse. The role of estradiol, and other gonadal hormones, on addiction-like behaviors in males, however, is not well understood. Research from the Becker laboratory finds that estradiol does not enhance cocaine taking behavior of castrated male rats. The current experiment investigated the effects of estradiol receptor (ER) activation and inactivation on susceptibility to drug preference in intact males. Rats were initially given access to a three-compartment conditioned place preference (CPP) apparatus. A biased design was utilized to assign the initially non-preferred side with drug. For eight consecutive days, rats were conditioned every other day with cocaine (10 mg/kg, i.p.) or vehicle (saline) immediately before being placed into the apparatus. On day ten, animals had access to the entire chamber and their overall CPP was re-analyzed. Rats received intra-cannula administration of ICI182,780:Cholesterol (1:10) into dorsal striatum or nucleus accumbens constantly during conditioning and during the final test session. The control group received intra-cannula administration of Cholesterol only. Results indicate that ICI182,780 treatment in either location reduced the time spent in the drug-paired chamber on test day, compared to cholesterol treated males, or ICI182,780 or cholesterol treated females. These data indicate that ER manipulation in male rats, but not females, can affect CPP for cocaine. ICI182,780 is a non-specific G-protein ER (GPER1) agonist as well as an ER α/β antagonist, therefore, a follow up experiment was needed to tease apart these mechanisms. Experiments using G1, a GPER1 specific agonist, were conducted to determine whether the cocaine CPP can be modulated by GPER1 activation. Results will be presented at the meeting. These results indicate that while estradiol enhances drug-taking in females, in males it reduces CPP. These findings further our understanding of how ERs may play a crucial role in sex differences in the formation of drug preference. This study was funded by NIDA: R01DA039952 to JBB

4. Localizing the role of Homer2 in regulation of methamphetamine reinforcement. C.N. Brown, E.K. Fultz, S. Ferdousian, S. Rogers, E. Lustig, T. E. Kippin, K. K. Szumlinski. University of California, Santa Barbara. Despite profound public health ramifications of methamphetamine (MA) abuse, neural mechanisms underlying the transition from early stages of drug use to addiction are poorly understood. Previous work indicates increased motivational valence and reinforcement for MA in *Homer2* knockout mice, implicating this glutamate receptor related, post-synaptic scaffolding protein in neuroplasticity of early MA use. To probe these results with developmental and anatomical specificity, Homer2b expression was bidirectionally manipulated in the nucleus accumbens (NAC) core or shell using an adeno-associated viral vector (AAV) carrying either short hairpin RNA (shRNA) to knockdown, or complementary DNA (cDNA) to increase Homer2 expression. First, MA-induced place conditioning procedures were employed to gauge the effects of manipulating Homer2b levels upon MA's motivational valence. Then, operant conditioning procedures were utilized to examine changes in MA reinforcement and intake. We observed neuroanatomically selective effects of intra-NAC shRNA-Homer2b, with core infusions promoting and shell infusions attenuating MA reward sensitivity in C57BL/6J mice. Reversing the MA phenotype of *Homer2* knockout mice, using AAV-cDNA, revealed inconsistent effects that conflict with data observed in knockout and shRNA-infused animals. Ultimately, these results indicate that while Homer2 seems to have a global inhibitory role in regulating MA reinforcement, its influence cannot be localized to the NAC sub-regions, implicating other sites of action and emphasizing the importance of investigating not only one isolated brain region, but rather the connectivity between regions. Therefore, future work will focus on characterizing

the role of sub-circuits between the prefrontal cortex and the NAC in regulating MA reinforcement using chemogenetic techniques.

5. Within animal comparison of neuronal ensembles engaged by novelty and drug reward. Natalie N Nawarawong, Megan Slaker, and Christopher M Olsen. Neuroscience Research Center and Department of Pharmacology & Toxicology, Medical College of Wisconsin, Milwaukee, WI. Novelty seeking is a personality trait associated with an increased vulnerability for substance abuse. In rodents, elevated novelty seeking has been shown to be a predictor for elevated drug self-administration and compulsive use. While previous studies have shown that both novelty and drugs of abuse have actions within similar mesocorticolimbic regions, little is known as to whether the same neurons are engaged by these two stimuli. In this project, we wanted to determine the neuronal ensembles associated with novelty and cocaine in the Nucleus Accumbens (NAc) and the Prefrontal Cortex (PFC), brain regions implicated in reward processing. For this comparison, we used the TetTag H2B-EGFP mouse model (a dual transgenic reporter line that allows for long lasting temporally controlled tagging of active neurons). All animals were maintained on chow containing doxycycline (dox, to inhibit tagging) prior to the start of the experiment. When dox was removed, experimental animals were exposed to a novel open field and novel objects to induce EGFP tagging. Three days following the resumption of dox, experimental animals were administered a single cocaine injection in a habituated chamber and perfused two hours after the injection. This was a balanced 2x2 design, where control groups adhered to the same experimental timeline and either received novelty or cocaine alone, or neither (homecage and saline). To visualize cocaine-activated neurons, we performed immunohistochemistry for Fos (a marker of neuronal activity) and utilized the TetTag EGFP reporter to detect novelty-activated neurons. While we found significantly more Fos activated neurons in the NAc core and shell, it was only in the NAc shell that there was a significantly greater proportion of EGFP reactivated neurons in the novelty and cocaine exposed animals compared to animals receiving either novelty alone, cocaine alone, or neither. To date, this data suggests that the NAc core may be important in mediating the effects of the cocaine reward, while the NAc shell may play an important role in novelty and cocaine reward processing by activating a similar network of neurons. Ongoing experiments are investigating if similar trends are observed with different classes of drugs of abuse. Acknowledgements: NIH R00 DA026994. NIH R01 DA042792. Research and Education Initiative Fund, a component of the Advancing a Healthier Wisconsin. Endowment at the Medical College of Wisconsin. Neuroscience Research Center, Medical College of Wisconsin.

6. What is the role of subcutaneous single injection on the behavior of adult male rats exposed to drugs? Slamberova, Romana; Nohejlova, Kateryna; Ochozkova, Anna; Mihalcikova, Lydia. Charles University, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic. Psychostimulants as well as cannabinoids have been shown to affect a great variety of behaviors in both, humans and laboratory animals, in a serious manner. Our previous studies repeatedly demonstrated that control groups with saline injection(s) have displayed changes in different behavioral tests when compared to absolute controls (without any injection). Therefore, our present study has set three aims: (1) to evaluate the effect of three different psychostimulant drugs; (2) to evaluate the effect of three doses of delta9-tetrahydrocannabinol (THC); and (3) to evaluate the effect of saline, ethanol solvent or injection per se (sham) on spontaneous behavior of adult male rats. LABORAS test (Metris B.V., Netherlands) was used to examine spontaneous locomotor activity and exploratory behavior in unknown environment during 1 hour. In Experiment 1, psychostimulant drugs were tested: single subcutaneous (s.c.) injection of amphetamine (5mg/kg), cocaine (5mg/kg) and MDMA (5mg/kg) was applied prior to testing. Control group received s.c. saline injection in the same volume (1 ml/kg). In Experiment 2, three doses of THC (1; 2 and 5 mg/kg, s.c.) were examined. As a control s.c. injection of solvent (ethanol) was used. In Experiment 3, injections of saline and ethanol were compared to group with sham s.c. injection and to group of absolute control without any injection. Our results demonstrated that (1) all psychostimulants increased the locomotion, distance traveled and the velocity, while decreasing the duration of immobility of adult male rats relative to saline controls. The most prominent effect was found after MDMA

injection. (2) The effect of THC was dose dependent and was the most apparent within the first 10 minutes of the LABORAS test. (3) As a matter of the effect of injection: absolute controls (without injection) when compared to animals injected with ethanol, saline or sham displayed lowered time spent in immobility, traveled longer distance and displayed increased velocity. In conclusion, our data showed different changes in behavior of adult male rats after application of either psychostimulants or cannabinoids. Our findings also suggest that not only drugs, but also single injection per se affects behavior of laboratory animals in unknown environment. This effect seems to be associated with acute stress reaction. Supported by: Progres Q35, GACR 18-03806S, GAUK 850317

7. Optogenetic Inhibition of Methamphetamine-Seeking in Rats. Rebecca Cordie, Lisa M. McFadden. Division of Basic Biomedical Sciences, University of South Dakota, Vermillion, SD 57069. Methamphetamine (METH) is a highly addicting psychostimulant. There is a high prevalence of use in the United States that leads to an increasing number of METH related fatalities. There are currently no pharmacological treatments available for METH addiction. To help guide the development of treatment options, it is important to understand changes underlying METH addiction in the brain. Two key brain regions in the reward circuit of the brain are the medial prefrontal cortex (mPFC) and the nucleus accumbens (NAcc). Glutamatergic neurons project from the mPFC to the NAcc to modulate its activity. The purpose of this study was to investigate this pathway and its role in METH-seeking behavior in male and female rats. Male and female rats were allowed to self-administer METH and underwent extinction and two reinstatement sessions. Reinstatement sessions were counterbalanced such that optogenetic inhibition of the mPFC neurons only occurred during one reinstatement session. Results revealed an increase in METH consumption during self-administration in males and females animals. Further, during extinction, this drug-seeking behavior decreased as training progressed. When animals reinstated with the laser off, female rats exhibited significantly higher drug-seeking behavior. However, when the optogenetic inhibition was applied to the mPFC, both males and females significantly decreased drug-seeking. In conclusion, excitatory activity in mPFC pathway may play an important role in drug-seeking behavior related to METH addiction in both males and females. Research support: NIDA grant R25-DA033674 along with the NIH grant DA036012.

8. The role of the serotonin 1B receptor system in the development of methamphetamine-induced sensitization. Yuki Moriya1,2; Yoshiyuki Kasahara1; Yoko Hagino2; F. Scott Hall3; René Hen4; Kazutaka Ikeda2; George R. Uhl5; Ichiro Sora1, 6 1Department of Biological Psychiatry, Tohoku University Graduate School of Medicine, Sendai, Japan. 2Department of Psychiatry and Behavioral Sciences, Tokyo Institute of Psychiatry, Tokyo, Japan. 3Department of Pharmacology, Toledo University, USA. 4Department of Neuroscience and Psychiatry, Columbia University, New York, NY 10032-2695, USA. 5Research Service, New Mexico VA Healthcare System, Albuquerque, NM, USA 6Department of Psychiatry, Kobe University, Graduate School of Medicine, Kobe, Japan. OBJECTIVE: Methamphetamine (METH) is a powerful addictive stimulant drug that activates in the brain, resulting in behavioral alterations including sensitization and dependence. Monoaminergic systems, including those that act via 5-hydroxytryptamine 1B (5-HT1B) receptors, may play key roles in regulating locomotor stimulation that follows acute and/or chronic METH administration. We have previously found that the behavioral sensitization was normalized in serotonin transporter knockout mice by pre-treatment with a selective 5-HT1B receptor antagonist. Moreover, the behavioral sensitization to METH (1 mg/kg) was enhanced in homozygous 5-HT1B receptor knockout (5-HT1B-/-) mice compared to wild-type (WT) mice, but was attenuated in heterozygous 5-HT1B receptor knockout (5-HT1B+/-) mice compared to WT and 5-HT1B-/- mice. We now report attempts to seek alterations inexamination of extracellular serotonin (5-HTex) levels following administration of METH that might correlate with levels of locomotor sensitization in WT and 5-HT1B KO mice. METHODS: In vivo Microdialysis technique and HPLC-ED were used to measured the effects of acute METH injection upon extracellular dopamine (DAex) and serotonin (5-HTex) levels in 1) the striatum and 2) the nucleus accumbens in awake WT, 5-HT1B+/-, and 5-HT1B-/- mice. RESULTS: In vivo microdialysis demonsratesdemonstrates that acute administration of METH (1 or 3mg/kg) increases extracellular dopamine (DA) levels in the caudate putamen (CPu) and nucleus accumbens (NAc) of wildtype WT and knockout KO mice. In the NAc, both 1 and 3 mg/kg METH doses induced

larger DA increases in knockout KO than in WT mice. Basal NAc dialysate DA concentrations were also higher in knockouts KO mice than in WT mice, although we identified no differences in CPu. Nevertheless, in CPu the effect of METH was larger in 5-HT1B-/- mice than in WT mice at the 3 mg/kg, but not at 1 mg/kg. CONCLUSIONS: In comparing neurochemical differences in homozygous 5-HT1B KO vs WT mice, we found that the increased locomotor sensitization in 5-HT1B-/- mice is associated with greater effects of METH on extracellular DA and 5-HT levels. By contrast, in 5-HT1B +/- mice the relative increases in 5-HTex are greater than those for DA compared to WT mice. Extracellular 5-HT levels may contribute to the differential effects of METH in heterozygous and homozygous 5-HT1B knockout KO mice on locomotor activity. Acknowledgements: Grant-in-Aid for Research Activity start-up: 16H07463. Japan Society for the Promotion of Science (JSPS): 254961.

9. A ketogenic diet improves biconditional association task acquisition and decreases anxiety-like behavior in young and aged rats. Abbi Hernandez, Keila Campos, Leah Truckenbrod, Brianna Moon, Quinten Federico, Sara N. Burke. University of Florida. Cognitive impairment and increased incidence of anxiety often accompany advanced age. Although these age-associated disruptions can impair the ability to independently perform activities of daily living and decrease quality of life for older adults, the neurobiological mechanisms of these changes remain unknown. Among the first brain regions to be affected by aging are the medial temporal lobe (MTL) and prefrontal cortex (PFC), both of which must interact to support higher cognitive function. While many of the age-related biochemical alterations in MTL and PFC are uncorrelated, both of these structures are particularly vulnerable to age-related decreases in both neuronal glucose metabolism and mitochondrial function. These changes can affect cognitive processes, which require ATP bioavailability during task performance. While acute glucose application is restorative of several cognitive behaviors in rodents, long-term glucose consumption increases the risk of obesity and diabetes, which themselves eventually lead to cognitive impairment. Rather than trying to restore insulin/glucose signaling, an alternative approach for improving cognition in advanced age is to alleviate the dependence on glycolysis for cellular metabolism with a ketogenic diet (KD), which is a high-fat, low-carbohydrate diet that utilizes ketone bodies derived from fat for metabolism. Our previous work has shown that 12 weeks of a ketogenic diet (KD) can decrease body fat percentage and restore glutamate transporter protein levels within the hippocampus, suggesting that the KD may be beneficial for the aged brain. This current study aimed to see if the same diet could improve cognitive function on a task that is known to require MTL-PFC interactions. Young (4 month) and aged (20 month) rats were placed on a KD or control diet (CD) for 12 weeks prior to testing on several behavioral tasks, including a biconditional association task (BAT). Regardless of age group, rats on the KD outperformed CD rats on the BAT by making fewer mistakes on the object-in-place rule within the same number of training sessions. KD rats also exhibited less anxiety-like behavior, demonstrated by willingness to enter the open arm of the maze more readily than CD rats. Furthermore, CD rats were significantly less likely to correctly make an object choice in the open arm than the closed arm, but KD rats were not. These data suggest that KDs are a therapeutic option for the treatment of age-related cognitive decline.

10. Aging dependent changes across behavioral phenotypes vary with sex and strain in genetically diverse mouse populations. Torrian L. Green[1], Shawn Winter[1], Emily Viands[1], Gabriella Little[1], Laura C. Anderson[1], David E. Harrison[2], and Stacey J. Sukoff Rizzo[1]. 1The Jackson Laboratory, Neurobehavioral Phenotyping Core, Center for Biometric Analysis, Bar Harbor, Maine, USA. 2The Jackson Laboratory, Bar Harbor, Maine, USA. Genetic diversity contributes to variations in healthy aging including the relationship between chronological age and biological age. Several studies in mice have aimed to identify the most translational measures that reflect healthy aging but have been limited to primarily mice of the inbred C57BL/6J strain. The present studies aimed to evaluate aging related phenotypes in male and female mice of the genetically diverse HET3 population compared to aging C57BL/6J mice. HET3 mice are F1 offspring of females from a hybrid BALB/cJ x C57BL/6J background crossed to males from a hybrid C3H/HeJ x DBA/2J background; resulting in a four-way cross that provides a high level of genetic diversity (Flurkey et al. 2010). Male and female C57BL/6J and HET3 mice were evaluated in cross-sectional studies with age ranges from young adult (2-7 months) to advanced age (25-33 months). As expected there was

an age-dependent increase in frailty scores in both males and females across genotypes with inversely correlated reductions in core body temperature. C57BL/6J and HET3 mice demonstrated age-dependent deficits in grip strength with earlier onset in females relative to males. For motor alterations, home-cage wheel running was more sensitive at detecting age-related deficits compared to the open field. Specifically, while male C57BL/6J demonstrated age-dependent reductions in open field activity before 12 months of age, this was not observed in female C57BL/6J mice or HET3 males or females before advanced age. Interestingly, age-dependent reductions in activity were observed for wheel running measures across genotypes before 12 months of age; with the onset of the reduction in activity observed earlier in males than females. Age-dependent changes in vision and hearing as measured by optokinetic function and acoustic startle decibel response curves, respectively, were detectable as early as 12 months of age in males and females across genotypes with significant impairments by 24 months of age. Taken together the present studies demonstrate that aging related phenotypes vary with genetic diversity and sex, and underlie the importance that behavioral phenotypes across mouse strains are not generalizable. Further, understanding the trajectory of normal aging phenotypes provide insight to potential confounds such as impaired motor activity, vision, and hearing which are often required for the evaluation of cognitive assessments in aging mouse models.

11. Behavioral characterization of genetically diverse mouse populations: Implications for improving translation from mouse to human. Sukoff Rizzo, Stacey J[1]; Anderson, Laura C[1]; McGarr, Tracy[1]; Green, Torrian L.[1]; Winter, Shawn S[1]; Howell, Gareth R.[2]; Onos, Kristen D2. [1]The Jackson Laboratory, Neurobehavioral Phenotyping Core, Center for Biometric Analysis, Bar Harbor, Maine, USA. [2]The Jackson Laboratory, Neurobehavioral Phenotyping Core, Center for Biometric Analysis, Bar Harbor, Maine, USA. In an effort to improve translatability of mouse models to human diseases caused by complex etiologies, researchers are now beginning to incorporate panels of genetically diverse mouse populations. The Collaborative Cross (CC) mouse populations were generated by cross-breeding eight inbred strains of mice that include the two standard strains used in genome engineering, C57BL/6J, and 129S1/SvlmJ, the inbred A/J strain with high predisposition for developing cancer, two models of diabetes, NOD/ShiLtJ (Type 1) and NZO/HlLtJ (Type 2), and three wild-derived strains, CAST/EiJ, PWK/PhJ and WSB/EiJ. Together, these strains capture a diverse spectrum of genetic heterogeneity similar to what is present in the human population. In line with this genetic diversity, it is expected that these mouse populations would yield behaviors divergent from the typical performance of C57BL/6J mice in standard behavioral assays. Therefore, the aim of the present set of studies was to evaluate male and female mice of each of the eight strains that comprise the CC in a battery of behavioral tests. Adult male and female mice (n=8 per sex per strain) were evaluated in assays of motor and exploratory behaviors, anxiety related behavior, cognitive behaviors, vision, hearing, and motivation. As expected, relative to C57BL/6J mice, there was a spectrum of behavioral performance across each assay with clear reductions in exploratory behaviors in 129S1/SvlmJ mice, and high levels of activity in the wild-derived strains. These data provide insight for researchers aiming to employ genetically diverse mouse models in their testing and importantly demonstrate the lack of generalizability of sex and strain to behavioral performance in male C57BL/6J mice.

12. Androgen receptors and Histone Variant H2A.Z interact to regulate fear memory. FiryalRamzan[1], AmberB.Azam[2], CindyTao[1], KlotildaNarkaj[2], GildaStefanelli[1], D.AshleyMonks[1], IvaB.Zovkic[1]. 1 Psychology Department, University of Toronto, 2 Cell and Systems Biology, University of Toronto. Hormones have a significant effect on fear memory. While much is known about ovarian steroid hormones (e.g. estrogen) facilitating contextual fear conditioning in mice, much less is known about the role of androgens (e.g. testosterone) and the androgen receptor (AR) in memory formation. Previous literature shows mixed results, with testosterone leading to either a reduced or an enhanced contextual fear response. Using transgenic mice overexpressing AR, we showed that AR overexpression impairs fear memory. Gonadectomy eliminated group differences between AR-overexpressing and WT males, implicating testosterone as a negative regulator of fear memory through actions on AR. Further,

treatment with the AR-blocker flutamide increased fear memory, suggesting that AR negatively regulates fear memory. In addition, we showed that expression of H2A.Z, a memory suppressor identified in our lab, is increased in AR overexpressing mice, prompting us to investigate AR regulation in H2A.Z conditional knockout mice. In contrast to AR overexpression, H2A.Z depletion results in increased fear memory and decreased AR expression in area CA1 of the hippocampus. Castration DHT (dihydrotestosterone) replacement resulted in genotype-specific effects on fear memory, pointing to an interaction between H2A.z and AR. We also find corresponding changes in gene expression of genes encoding for synaptic proteins and memory-related genes. These results suggest a role of AR in modulating fear memory through interactions with nuclear histone proteins. This is a novel finding that we plan to expand to further understand the neuronal mechanisms through which this occurs. These studies were supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Grant and Connaught Fund awarded to Dr. Iva Zovkic, an NSERC Discovery Grant awarded to Dr. Ashley Monks, and an NSERC PGS-D to Firyal Ramzan.

13. Neural response to facial threats following buprenorphine administration in healthy young adults. Susan Malcolm-Smith[1], Lindie du Plessis[1], Ernesta Meintjies[1], Jonathan Ipser[1], Mark Solms[1], Kevin G.F. Thomas[1], Dan J. Stein[1] and Jack van Honk[1,2]. 1 University of Cape Town, South Africa; 2 Utrecht University, Netherlands. Manipulation of the endogenous opioid system changes behavioural responses to social threat in rodents and humans. In rodents, experience of early social stressors is associated with long-term opioid dysregulation alongside changes in stress responsivity, but this relationship is not well established in humans. In an opioid manipulation study (with buprenorphine, a mixed mu-opioid agonist and kappa-opioid antagonist) we used fMRI to examine neural responses to threatening facial expressions, in healthy young adults with varying exposure to early social trauma. We expected that neural responses to social threat would be reduced after buprenorphine, especially in those with high levels of early social trauma. Based on the literature on the neural processing of emotional faces, the fusiform gyrus and amygdala were used as regions of interest (ROIs). Methods: A double-blind, placebo-controlled, crossover design was implemented. Participants (N = 22; 9 females; mean age 21.6 ± 2.3) underwent fMRI scanning on both buprenorphine and placebo during a passive viewing task featuring dynamically morphing facial expressions (anger and fear for social threat, happiness as a positive control). Exposure to early social threat was assessed using the Childhood Trauma Questionnaire-Short Form (CTQ-SF). Employing BrainVoyager QX, whole-brain group analyses were performed with a random effects analysis of variance using the general linear model with predictor time courses for the three emotional epochs on and off buprenorphine, convolved by the standard hemodynamic response function. Regions were identified where changes in activation for each emotional condition on medication compared to placebo significantly correlated with CTQ-SF scores. Posthoc connectivity analyses between fusiform gyrus and amygdala were conducted. Results: Change in activation following buprenorphine in response to threatening facial expressions was correlated with CTQ-SF scores in the fusiform gyrus for both threatening emotions. The effect was also present in the inferior occipital gyrus for fear and the posterior cerebellum for anger. Connectivity between the fusiform gyrus and amygdala was significantly increased after buprenorphine. Conclusion: A single dose of buprenorphine attenuated neural responses to threatening social signals, and increased connectivity between amygdala and fusiform gyrus. Opioid manipulation with buprenorphine may have anxiolytic effects by down-regulating neural responses to social threats in the fusiform gyrus likely by way of the amygdala and particularly in those exposed to early social trauma.

14. Prefrontal function in fear and avoidance: From reaction to action. Maria M. Diehl[1], Christian Bravo-Rivera[1,2], Jose Rodríguez-Romaguera[1], Pablo A. Pagán-Rivera[1], Anthony Burgos-Robles[4], Jorge Iravedra-Garcia[1], Fabiola Gonzalez-Diaz[1], Gregory J. Quirk[1] 1Department of Psychiatry, University of Puerto Rico School of Medicine, San Juan, PR 00936 2Department of Neurobiology & Anatomy, University of Puerto Rico School of Medicine, San Juan, PR 00936. Much is known about the neural circuits of conditioned fear and its relevance to understanding anxiety disorders, but less is known about other anxiety-related behaviors such as active avoidance. Using a tone-

signaled, platform-mediated active avoidance task, we observed that pharmacological inactivation of the prelimbic prefrontal cortex (PL) delayed the initiation of avoidance. However, optogenetic silencing of PL neurons did not delay avoidance. Consistent with this finding, inhibitory, but not excitatory, responses of rostral PL neurons to the tone were correlated with the initiation of avoidance. To oppose inhibitory responses, we photoactivated rostral PL neurons during the tone to maintain pre-tone firing rate. Photoactivation of rostral PL (but not caudal PL) neurons at 4 Hz (but not 2 Hz) delayed or prevented avoidance. These findings suggest that the initiation of active avoidance requires inhibitory neuronal responses in rostral PL, and underscores the importance of designing behavioral optogenetic studies based on neuronal firing patterns. Ongoing studies are examining whether projections of rPL to the ventral striatum or baslolateral amygdala are necessary for active avoidance using optogenetic techniques.

15. Distinguishing between the contributions of depletion of processing resources and increases in opportunity costs to decline in attentional performance. Kyra B. Phillips, Lauren Rysztak, and Martin Sarter. Performance on sustained attention tasks declines over time and, more severely, in response to distractors and other performance challenges. Traditionally, such performance decline has been interpreted as reflecting depletion of cognitive resources. However, resource depletion models cannot explain invigorated performance following task switches or increased incentives to perform. An alternate hypothesis for this decline proposes that performers compute cost/benefit calculations for staying on task versus engaging in alternative action, termed opportunity costs. Increases in opportunity costs are subjectively experienced as increasing boredom, loss of motivation to perform, and fatigue. Thus, task performance declines and alternative action becomes increasingly attractive. Here we employed behavioral manipulations of attentional performance in rats to test conflicting predictions derived from these two theoretical perspectives. Male and female rats were trained on a sustained attention task (SAT) containing pseudorandomized cued and non-cued trials, requiring the reporting of cues as well as non-cue events via separate levers. In addition, rats performed several modified versions of SAT: SAT with 1) shortened intertrial interval (ITI) periods, 2) longer ITI periods, and 3) sequences of repeated trial types (during which only cued or non-cued trials are given). Importantly, the two competing perspectives predict opposed outcomes of these task manipulations: Shorter ITIs are thought to tax processing resources because of greater trial density but may decrease opportunity costs partially due to greater reward density. Inversely, longer ITIs are predicted to reduce the demand on processing resources while increasing opportunity costs. Further, trial repetition should not tax attentional resources, in part as the rat does not need to switch between response rules and levers, but it should elevate opportunity costs, partly because the monotony of repeated cue (or non-cue) processing and single lever pressing. The outcomes of these manipulations are being determined in rats with relatively poor versus relatively high cholinergic-attentional capacities (sign versus goal trackers, respectively) as the former may more effectively reveal effects of task manipulations. Defining the cognitive and neuronal mechanisms mediating attentional decline is crucial for developing treatments of the cognitive instabilities that typify a wide range of neuropsychiatric disorders.

16. Peripheral inflammation induces acute attentional impairments in rats. Yegla, B. & Foster, Department of Neuroscience, McKnight Brain Institute, University of Florida, Gainesville, FL. Aging is characterized by increased inflammation, which correlates with cognitive decline. Activation of the peripheral immune system via acute lipopolysaccharide (LPS) injection elicits deficits in learning, spatial memory, and cognitive flexibility, with middle aged rats displaying enhanced impairment. Little is known of inflammation's impact on vigilance, or, if systemic inflammation, which more closely models aging conditions, impairs attentional function. Thus we examined the impact of chronic LPS injections in young and middle-aged rats on the 5-choice serial reaction time task (5-CSRTT), expecting attentional deficits with chronic LPS treatment and greater disruption in middle aged rats. 4- and 12-month-old Fischer-344 rats were food restricted and trained on the 5-CSRTT, which requires continuous monitoring of a light cue (duration: 10, 2.5, 0.5s) occurring in one of five holes and nose poking the lit hole. Once rats reached criterion (>50% correct on each signal duration, <10% omissions

for 5 consecutive days) they were injected weekly with LPS (1mg/kg, i.p.) 48hrs before the task. Attentional capacity was assessed as a weekly average across four weeks. Rats were perfused and the prefrontal cortex (PFC), which contributes to attentional performance, was assessed for activated microglia (Iba-1) and astrocytes (GFAP). After the first LPS injection, rats exhibited an exaggerated sickness response, with fewer initiated trials during the first week (interaction: $F1.5,36.7=8.89$, $p=.00$). Average correct responses did not significantly vary by age or treatment ($p>0.05$); however, for the shortest signal duration, aged LPS-injected rats displayed greater attentional deficits during the first week ($p=0.05$). All LPS-injected rats exhibited longer correct ($F1,18=6.75$, $p=.02$) and incorrect response latencies ($F1,18=12.29$, $p=.003$), despite no change in food retrieval latency, suggestive of LPS-induced cognitive slowing. In addition to attentional deficits, smaller, activated microglia in the PFC were observed after chronic LPS treatment ($p=.05$). Compared to a separate cohort of non-food-restricted rats showing a significantly worse prefrontal inflammatory profile after LPS treatment, however, caloric restriction may have mitigated the effects of chronic peripheral inflammation. Thus, peripheral inflammation impaired cognitive processing acutely but not chronically, with middle aged rats exhibiting greater attentional deficits under challenging conditions.

17. Effects of infusions to the medial prefrontal cortex of an orexin-2 receptor antagonist on attention. Blumenthal, Sarah; Tapp, Austin; Maness, Eden; Burk, Josh1. College of William and Mary. Orexin neurons project to a number of brain regions that are implicated in attentional performance, including to the medial prefrontal cortex (mPFC). In particular the right mPFC specifically has been found to be crucial for attention. Orexin receptor blockade in the basal forebrain impairs attentional performance, whereas orexin A administration can be beneficial under some conditions. However, the role of mPFC orexin receptors in attention has not been well-characterized. Based on the results from experiments in the basal forebrain, orexin receptor blockade was hypothesized to impair attentional performance, particularly in the right hemisphere. Two orexin receptor subtypes exist, orexin 1 and orexin 2 (Ox1R and Ox2R, respectively). While the role of Ox1Rs in attention has been examined in several studies, the contribution of Ox2Rs has not been assessed in such detail. The present experiment examined the effects on attentional performance of an Ox2R antagonist, TCS-OX2-29, in the left or right mPFC. Rats were trained in a two-lever sustained attention task that required discrimination between visual signal and no signal trials. Guide cannula were implanted into the left or right mPFC and, after recovery and re-establishing baseline performance, TCS-OX2-29 was intracranially administered (0nM, 1nM, 10nM, 20nM). The results support our hypothesis in that high doses of the Ox2R antagonist impair attention. However, attention was enhanced at the lowest dose of the drug. We speculate that mild antagonism of Ox2Rs may increase receptor sensitivity for subsequent orexin transmission, leading to improvements in attention.

18. Interaction of rapid estrogenic effects and oxytocin in the mediation of recognition memory. Pietro Paletta[1], Joshua A. Smit[1], Andrila E. Collins[2], & Elena Choleris[1]. 1Department of Psychology and Neuroscience Program, University of Guelph, ON, Canada, 2Department of Biological Science, University of Guelph, ON, Canada. Social recognition (SR) is the ability to distinguish between conspecifics and is important for the development of social bonds and other aspects of social life. Both estrogens and oxytocin (OT) have been implicated in mediating SR. When the genes for the estrogen receptors a and b (ERa and ERb) were each knocked out SR was impaired. Similarly, when the genes for OT or the OT receptor (OTR) were knocked out SR was also impaired, suggesting that both estrogens and OT are needed for SR and that there could be an interaction between them. This interaction was hypothesized to occur through estrogens binding to their receptors in the paraventricular nucleus (PVN) to facilitate the production and release of OT which would then be sent to the medial amygdala to bind to the OTR and facilitate SR. We have tested whether this is accurate using a rapid SR paradigm, where we administered 17b-estradiol (E2) into the PVN followed by habituation phases where 2 stimulus mice were introduced to the experimental mouse. This was followed by a test phase where 2 stimulus mice were introduced again, one that was the same from the habituation phase and the other that was novel. If the experimental mouse investigates the novel stimulus mouse more than the other, it would suggest that they recognize the

familiar mouse and that SR occurred. We found that E2 was able to facilitate SR when tested within 40 minutes of its administration into the PVN. We next administered a subeffective dose of an OTR antagonist, that is not able to block SR by itself, into the medial amygdala to see if it could block the rapid facilitative effect of E2 administered into the PVN on SR. We found that the OTR antagonist in the medial amygdala was able to block the rapid facilitative effects of E2 in the PVN, suggesting that estrogens interact with OT to rapidly facilitate SR. We are also investigating whether other types of memory, like object recognition, can be similarly facilitated by this estrogen/OT interaction. We are using a similar recognition paradigm described above however instead of using mice as the stimuli, objects are used instead. We are testing whether E2 in the PVN can similarly facilitate object recognition and whether the OTR antagonist in the medial amygdala can block object recognition. If we find these results it would suggest that this rapid estrogen/OT interaction can affect not just social recognition, but other types of memory as well.

19. The Rapid Effects of Hippocampally-synthesized Estrogens on Recognition Learning in Ovariectomized Mice. Theresa K. Martin BAH, Lauren King, Melissa Klemens & Elena Choleris Ph.D. University of Guelph, Department of Psychology and Neuroscience Program, Guelph, ON, Canada. Estrogens are known to modulate cognition via very rapid and delayed mechanisms. Estrogenic action in the dorsal hippocampus has been implicated in rapidly modulating short-term and long-term recognition memory (Phan et al. 2015; Tuscher et al., 2016). Intriguingly, the hippocampus is capable of synthetizing its own estrogens. The rapid facilitation of short-term recognition memory by exogenous estrogens in the dorsal hippocampus (Phan et al., 2015), suggests endogenous, hippocampally-synthesized estrogens may be implicated. Here, we administered either 0.01, 0.05 or 0.1μg/μL of Letrozole, an inhibitor of the estrogen-synthetizing enzyme aromatase or 2% dimethyl sulfoxide vehicle to the dorsal hippocampus of 2-month old ovariectomized CD1 mice 15-minutes before the learning of either a social or an object recognition task. First, an experimental mouse was able to repeatedly explore either a conspecific or an object for three 4-minute habituations. These phases were separated by 3-minute rest periods, with no stimuli present. Second, after a 3-minute retention interval the mouse underwent a 4-minute test where one of the repeated stimuli was switched-out for a novel one. The test was completed within 40-minutes of treatment, thus targeting the effects of rapid regulation of estrogen synthesis. If hippocampally synthetized estrogens are necessary for the rapid enhancement of short-term recognition memory it was predicted that all Letrozole treated groups would not show recognition learning at test. The hypothesis was partially supported by our results, where groups treated 0.01 or 0.05μg/μL did not show recognition learning, whereas the 0.1μg/μL treated group performed like controls. The results were specific to performance in the learning tasks and were not secondary to changes in overall stimulus investigation. The lack of inhibitory effect of the 0.1μg/μL dose may be explained by alterations in other steroid hormones by the high dose of Letrozole. Overall, these results suggest that estrogens synthesized by the dorsal hippocampus are involved in rapid short-term recognition memory, where their decrease may lead to impairment at low concentrations of Letrozole, but recovery of short-term memory at the highest concentration, potentially via other steroidogenic mechanisms. These results may contribute to more effective hormone replacement therapies for cognitive deficits experienced by menopausal women.

20. Chronic treatment with Bifidobacterium (Longum, Breve, Infantis) modulates gene expression, neuronal function and structure in rat hippocampus. Mostallino, Maria Cristina[1]; Biggio, Francesca[2]; Talani, Giuseppe[1]; Locci, Valentina[1]; Sanna, Enrico[1,2]; Biggio, Giovanni[1,2] 1 Istituto di Neuroscienze, Consiglio Nazionale delle Ricerche, CNR, Cagliari; 2 Dipartimento di Scienze della Vita e dell'Ambiente, Università di Cagliari, Cagliari. It has been recently proposed that changes in microbiota alter the stress responses to the hypothalamic-pituitary-surrenal (HPA) axis, an effect that may involve the inhibitory neurotransmitter GABA, one of the first candidates in the modulation of emotional states. In our laboratory we studied in adult rats the long-lasting effect of a 1-2 months chronic treatment with a preparation of three different Bifidobacterium (Longum, Breve, Infantis) on GABAreceptor gene expression, GABAergic function in hippocampus as well as HPA axis sensitivity to acute foot-shock stress. Plasma

corticosterone (CTS) levels was measured in basal condition and after foot-shock stress of animals previously treated with bifidobacterium. Bifidobacterium treatment failed to changes foot-shock-induced increase of CTS levels when compared to vehicle group. Western blot and immunohistochemistry analysis showed that two months of bifidobacterium treatment reduced α1, α4, and δ GABAAR subunits expression while increasing γ2 subunit. Patch-clamp experiments performed in dentate gyrus granule cells (DGGC) showed no change in synaptic currents whereas the tonic component of GABAergic inhibition was significantly decreased. The latter data correlates with an observed increase of neuronal excitability measured in the same neurons of the dentate gyrus as well as with the reduction of δ subunit. The lack of bifidobacterium protective action towards acute stress worth a further consideration given that treatment was carried out in healthy animals suggesting that beneficial effects of bifidobacterium could better manifest themselves in organisms with an altered microbiota. These results, together with our more recent findings showing that chronic bifidobacterium increased the number of spines in CA1 pyramidal neurons and in the granule cells of dentate gyrus further support the crucial role of specific gut bacteria in the modulation of accordingly brain function. Accordingly, the concept of psychobiotics as new tools to be used in mental health has been recently suggested.

21. Reduction of GSK3β in the ventral hippocampus impairs development of psychostimulant-induced place preference and novel object location memory. Jeffrey L Barr, Xiangdang Shi, Michael E Zaykaner and Ellen M. Unterwald. Department of Pharmacology and the Center for Substance Abuse Research, Lewis Katz School of Medicine at Temple University, Philadelphia, PA 19140 USA. The ventral hippocampus regulates approach-avoidance behavior as a crucial component of the neural circuitry involved with appraisal of incentive value of outcomes and generation of appropriate behavioral responses to context. The formation of context-reward associations depends on the hippocampal-nucleus accumbens system, with the accumbens integrating contextual information from the hippocampus into reward-directed behaviors. Hippocampal glycogen synthase kinase 3beta (GSK3β) has been linked to the maintenance of synaptic plasticity in excitatory neurons and contextual memory retention and is involved in the reconsolidation of cocaine contextual reward memory. In this study, we examined the effects of targeted downregulation of GSK3β in the ventral hippocampus on a series of behavioral paradigms for assessing drug reward and familiarity discrimination. We used the Cre/loxP site-specific recombination system through bilateral stereotaxic delivery of an adeno-associated virus expressing Cre-recombinase (AAV-Cre) into the ventral hippocampus of adult mice homozygous for a floxed GSK3β allele (generously provided by Dr. J. Woodgett). Mice injected with AAV-Cre in the ventral hippocampus displayed diminished development of cocaine-conditioned place preference behavior but not morphine-place preference. Impaired object displacement detection was also observed, whereas GSK3β downregulation (60-70%) in the ventral hippocampus had no effect on novel object recognition. These results indicate that GSK3β signaling in the ventral hippocampus is differentially involved in the formation of place-drug reward association dependent upon drug class. Additionally, ventral hippocampal GSK3β signaling is important in detection of discrete spatial cues, but not recognition memory for objects. These results suggest that GSK3β signaling within the ventral hippocampus plays discrete roles in the modulation of place memory and contextual cues related to drug-reward.

22. Differential representation strategies for delay discounting in the hippocampus and medial prefrontal cortex. Akira Masuda[1,2], Chie Sano[1], Thomas McHugh[1], Shigeyoshi Fujisawa[1], Shigeyoshi Itohara[1]. 1 RIKEN, 2 Doshisha University. The hippocampus and medial prefrontal cortex (mPFC), which are critical regions for memory and prospecting future, have been repeatedly implicated as involved in delay discounting; however, the ir precise roles are poorly understood. Here we investigated neuronal coding of the hippocampal CA1 and mPFC during a delay-discounting decision making task in a T-maze, where delay lengths and reward amounts were changed in the arms across sessions. During the delay, the neuronal activities of the CA1 and mPFC were frequently dependent on the delay lengths. The population activity clearly discriminated the delay phase in CA1 but not in mPFC. The knockout of hippocampal NMDA receptor strongly damped the delay discounting and collapsed the population activity for the discrimination of delay phase in CA1. In addition, CA1 neuronal activities were

correlated with devaluation, that is, increase of delay duration and decrease of reward sizes, but mPFC neurons represented information of delay lengths and reward sizes independently. These results suggest that hippocampal neurons encode cost-benefit information in delay-discounting, while mPFC neurons encode information of delay and reward separately.

23. Corticotropin-Releasing Factor (CRF) Modulation of Distinct Prefrontal Cortex (PFC)-Dependent Cognitive Processes. Sofiya Hupalo and Craig W. Berridge. University of Wisconsin-Madison, Madison, WI 53706. The prefrontal cortex (PFC) plays a critical role in higher cognitive processes that support goal-directed behavior. PFC-dependent cognitive dysfunction is implicated in multiple psychopathologies, including ADHD. Recent evidence demonstrates that corticotropin-releasing factor (CRF) receptor activation within the PFC impairs, while blockade of PFC CRF receptors improves working memory performance in rats. One possible source of CRF for the cognition-modulating receptors are local CRF-synthesizing neurons, long known to be prominent in the PFC. To examine whether these neurons modulate PFC-dependent cognition, we used a dual viral vector system to express hM3Dq-coupled designer receptors (DREADDs) in PFC CRF neurons. Chemogenetic activation of PFC CRF neurons using the DREADD agonist, clozapine-N-oxide (CNO), robustly impaired working memory performance. Conversely, chemogenetic suppression of PFC CRF neurons improved working memory. CNO had no impact on working memory in control virus-treated animals. Moreover, the working memory-impairing actions of PFC CRF neuronal activation were blocked by local infusions of a CRF antagonist (D-Phe-CRF, 100 ng). Collectively, these observations indicate the working memory actions of PFC CRF neurons involve local CRF receptor signaling. To examine whether PFC CRF neurotransmission modulates PFC-dependent cognition more broadly, we also examined the effects of PFC CRF manipulations in a signal detection test of sustained attention. Chemogenetic activation of PFC CRF neurons similarly impaired sustained attention. These actions were blocked with systemic (NBI 35965, 1 mg/kg), but not intra-PFC (D-Phe-CRF, 100 ng) administration of CRF antagonists. When administered alone and at a higher dose (2.5 mg/kg), the CRF antagonist, NBI 35965, significantly improved sustained attention performance. Collectively, these observations demonstrate CRF neurons in the PFC exert potent modulatory actions on multiple PFC-dependent cognitive processes via different projection pathways. Importantly, the cognition-enhancing effects of CRF antagonists in both tasks of working memory and sustained attention mimic the pro-cognitive actions of ADHD medications. As such, CRF antagonists may represent a novel pharmacological approach for the treatment of ADHD and other disorders associated with PFC-dependent cognitive dysfunction.

24. Sex-differences in hippocampal dopamine release in association with social learning in mice. Richard Matta, Madison J. Russell, Cheryl L. Limebeer, Linda A. Parker and Elena Choleris. Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada, N1G2W1.
Social learning is the processes by which an animals learning is influenced by observing/interacting with a conspecific. The neurobiological mechanisms underlying social learning are slowly being examined. Initial studies using systemic treatments find that the neurotransmitter dopamine (DA) is involved in the social transmission of food preferences (STFP) in mice, whereby DA D1-type receptors regulate social learning, and D2-type receptors regulate feeding behavior in the STFP (Choleris et al., 2011). Follow-up studies aimed at deciphering possible brain regions of action underlying these systemic effects have been conducted. The ventral tegmental area has direct dopaminergic projections to the hippocampus—a brain region that has been implicated in the STFP. Using DA receptor antagonists, we have found that male mice rely only on dorsal hippocampal D1-type receptors, whereas female mice rely on both dorsal hippocampal D1-type and D2-type receptors in the STFP (Matta et al., 2016, 2017). The purpose of this study was to examine whether social learning in the STFP was associated with changes in dorsal hippocampal DA levels. Microdialysis and high-performance liquid chromatography methods revealed that male mice had greater hippocampal DA release than female mice during an olfactory exposure to a non-demonstrated novel food odour, a non-demonstrated social interaction, and the STFP. Furthermore, females showed lower hippocampal DA release (relative to baseline) during the novel food odour and social

stimuli exposures, whereas males showed greater hippocampal DA release during these exposures. Such sex differences in hippocampal DA release suggest that male and female mice process novel/social stimuli differently.

25. Acetylcholine signaling in the ventral tegmental area regulates motivation to work for a desirable reward in an effort-based decision-making task. Joshua L. Haight, Durga J. Rathi, Eric J. Nunes, and Nii A. Addy. Department of Psychiatry, Yale University, New Haven, CT. Motivation to work for life-sustaining needs is a core feature of human and animal behavior. In addition, a lack of motivation (i.e. anhedonia) is a main symptom of depression. Studies utilizing rodents have demonstrated that dopamine signaling along the mesolimbic pathway, from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), is an essential component of the neurobiology underlying motivated and depression-like behaviors. While the role of dopamine in these behaviors has been demonstrated, the question surrounding what VTA inputs drive these behaviors remains. It has been hypothesized that cholinergic inputs into the VTA are critical for mediating motivated behavior. Recently, our lab and others have shown that cholinergic signaling in the VTA is a powerful regulator of both VTA dopamine cell activity and dopamine release in the NAc. In addition, our lab has demonstrated that cholinergic signaling in the VTA can regulate the ability of sucrose- and cocaine-paired cues to motivate reward-seeking behaviors, as well as depression-like behavior in the forced-swim test and elevated plus maze. Here, we examine the role of cholinergic signaling in the VTA in the effort-based decision making task. In this task, subjects have a choice between consuming freely available rat chow, or pressing a lever on a fixed-ratio 5 schedule to obtain 45mg sucrose pellets, a more highly desired reward. Importantly, the motivation to work for sucrose pellets in this task is dependent on dopamine transmission in the NAc, and this model has been suggested as a proxy for measuring the anhedonia-like symptoms of depression in rodents. In this study, we assessed the effects increased cholinergic tone, which is known to produce depressive symptoms in humans, on behavior in the effort-related choice task. We found that systemic administration of physostigmine (0.125 mg/kg) decreased lever responding, with no effect on chow consumption, in both male and female rats. In addition, preliminary data indicates that bilateral physostigmine infusion (2ug per side) directly into the VTA also decreased lever responding, while leaving chow consumption intact. These results suggest that cholinergic signaling, potentially in the VTA, regulates the motivation to work for a desirable reward, without reducing the drive to eat freely available chow. In addition, this work suggests that VTA cholinergic signaling might be an interesting target for regulating anhedonia.

26. Calorie restriction and a viral mimic: Not a straightforward relationship. Kent, S., Kivivali L, Chong K, Kirby A. Department of Psychology & Counselling, La Trobe University, Melbourne, Australia. Calorie restriction (CR) extends mean and maximum lifespan in a variety of animals and we have previously demonstrated that CR dose-dependently attenuates lipopolysaccharide (LPS)-induced fever and sickness behaviour. LPS is a bacterial mimetic; however, few studies have explored this phenomenon utilising a viral mimic, such as polyinosinic:polycytidylic acid (poly I:C). The current study aimed to investigate whether a 50% CR for 28 days could attenuate poly I:C-induced fever and sickness behaviour. METHOD: C57BL/6J male mice implanted with biotelemetry devices were housed at 30 ± 2°C under a 12:12 LD cycle. In a pilot experiment increasing doses (500, 1000, 2000, and 5000 μg/kg) of poly I:C or vehicle were administered and core body temperature (Tb) and locomotor activity measured for 24 hours. In the main experiment mice with implanted biotelemetry devices were assigned to either ad libitum (AL; n = 16) or CR50% (n = 16) groups for 28 days. On day 29, either 5000 μg/kg poly I:C or vehicle was injected and sickness behaviour assessed for 24 hours. RESULTS: In the pilot experiment poly I:C induced a dose-dependent increase in Tb, with the largest dose (5000 μg/kg) resulting in a 1.62 ± 0.23°C Tb increase from baseline at 7 hours post-injection ($p = .016$), which was associated with reduced locomotor activity during the subsequent dark phase post-injection ($p = .001$). The main experiment demonstrated that CR partially attenuated poly I:C-induced fever and sickness behaviour . The AL group experienced a peak in Tb of 2.02 ± 0.22°C 7 hours post-injection compared to a 0.94 ± 0.27°C increase in the CR poly I:C at the same time post-injection ($p = .004$). Locomotor activity was reduced in the CR group only during the light phase ($p = .019$),

most likely due to decreased food-related anticipatory behaviour whereas activity declined in the AL group only during the dark phase post-poly I:C ($p = .002$). The CR and AL mice demonstrated similar responses after poly I:C on other sickness behaviour measures (weight loss and reduced food intake). CONCLUSION: Poly I:C evoked a partial sickness behaviour response in CR mice, indicating the subtlety different pathways utilised by viral mimics, compared to bacterial mimics like LPS, may be differentially impacted on by CR. Future research should investigate whether CR impacts on the number or activity of Toll-like receptors 3 and 4 that recognise viral and bacterial mimics.

27. Gonadal hormones mediate changes in adaptive choice and dopamine release in female rats. Yoest, KE[1], Shashlo, KE[1], Cummings, JA[1], Becker, JB[1]. University of Michigan. In female rodents, sexual receptivity is coordinated by cyclic changes in the release of gonadal hormones. Increases in estradiol (E2) and progesterone (P) during proestrus and estrus not only induce ovulation, but also modulate behaviors that increase the probability that the female will find a mate and reproduce. This includes changes in receptive behaviors, such as lordosis, as well as appetitive or proceptive behaviors, including motivation. Interestingly, the direction of these changes in motivation is dependent on the type of reward that is being pursued. While induction of sexual receptivity by E2 and P increases motivation for access to a male, motivation for food is decreased. We have hypothesized that these concurrent changes in motivation facilitate adaptive choice across the estrous cycle. Females bias their choice in favor of a reproductive partner when fertilization is most likely to occur, but for food when copulation will not result in impregnation. In order to test this hypothesis, we developed a novel paradigm to measure motivated choice between a palatable food reward and access to a male conspecific. Ovariectomized, hormone primed females were trained to respond for both food and sex on a fixed interval (FI) schedule. After training, unprimed and primed females were tested in a chamber that allows them to choose between food and sex while still requiring responding on the FI schedule for each reward. From this we can not only determine the impact of hormone priming on female choice for food or sex, but also how this is reflected by changes in motivation for each reward, as measured by the average number of responses made during each interval. We have found that induction of sexual receptivity by hormone priming biases choice toward sex over food, and this change is reflected by a decrease in motivation for food but an increase in motivation for sex. We predict that E2 and P mediate changes in motivation via modulation of dopamine (DA) release in response to rewards and reward paired cues. To test this hypothesis, we are using fast scan cyclic voltammetry (FSCV) to measure how changes in motivation for food and sex are accompanied by changes in phasic DA release within the nucleus accumbens. This work provides a novel framework for understanding how release of gonadal hormones over the course of the estrous cycle modulates nucleus accumbens DA signaling, as well as how this can be related to adaptive behavioral choice in females.

28. Prenatal alcohol exposure changes neuronal activations in brain regions mediating the interpretation of facial affect. Lindinger, N. M.[1], Jacobson, J. L. [1,2,4], Warton, C. [2], Malcolm-Smith, S.[3], Molteno, C. D.[1,2], Dodge, N. C.4, Robertson, F.[1], Meintjes, E. M.[1], and Jacobson, S. W[1,2,4.] 1Child Development Research Laboratory, Department of Human Biology, Faculty of Health Science, University of Cape Town, Cape Town, South Africa 2Department of Psychiatry and Mental Health, University of Cape Town Faculty of Health Sciences, Cape Town, South Africa 3ACSENT Laboratory, Department of Psychology, Faculty of Humanities, University of Cape Town, Cape Town, South Africa 4Department of Behavioural Neuroscience and Psychiatry, Wayne State School of Medicine, Wayne State University, Detroit, MI 48201, USA. During the development of social skills, interpretation of the affective message portrayed in facial emotions plays a critical role in providing feedback to social encounters and in promoting social interactions. Although deficits in the interpretation of affective facial expressions have been described clinically in FASD and documented among others on the “Reading the Mind in the Eyes” test, effects of prenatal alcohol exposure on the neural networks that mediate affective appraisal have not previously been examined. We administered a nonverbal event-related fMRI affective appraisal paradigm to 64 South African children (18 FAS/partial FAS (PFAS), 18 non-syndromal heavily exposed, 28 controls) on a Siemens 3T Allegra MR

scanner. Happy, sad, angry, fearful, and neutral faces and pixelated control images were presented sequentially. The child indicated whether the currently displayed face showed the same or different affect as the previous one. All groups activated the appropriate neuronal face processing networks. However, compared with controls, the FAS/PFAS group exhibited more extensive neural activations when processing neutral faces, which are considered more difficult to interpret than positive and negative faces. The FAS/PFAS group showed greater activations in the right orbito-frontal gyrus and right middle temporal gyrus, involved in the recognition of facial emotions; the left lingual gyrus, which is involved in visually processing emotional faces; and the posterior part of the inferior temporal sulcus, which is activated during the processing of social and emotional content. The FAS/PFAS group showed lower levels of activation during the processing of angry faces, notably in the right lingual gyrus, which is involved in the visual processing of emotional faces; the right superior temporal gyrus, which is involved in the encoding of facial expressions; the medial frontal gyrus, which is activated in response to happy and angry faces; and the dorsolateral prefrontal cortex, which is implicated in reappraisal processes during emotion regulation. Our findings suggest that children with FAS/PFAS recruit more extensive neural resources to interpret neutral faces but engage in less detailed analysis of more complex affective expression, particularly anger. Our data identify functional deficits in brain regions known specifically to mediate the interpretation of emotional stimuli and suggest that affective appraisal is a core deficit in FASD.

29. The development of Cntnap2-related deficits in auditory processing: Implications for neurodevelopmental disorders. Kaela E. Scott, Susanne Schmid, and Brian L. Allman. Department of Anatomy and Cell Biology, Western University, London, ON. The mammalian auditory system undergoes considerable development and experience-dependent plasticity in early life. This normal maturation, however, is perturbed in individuals with neurodevelopmental disorders, such as autism spectrum disorder (ASD). These maturational differences may lead to impairments in auditory processing, and ultimately underlie the communication deficits and altered reactivity to sensory stimuli associated with ASD. For example, individuals with mutations in the autism-linked gene, contactin-associated protein-like 2 (CNTNAP2), experience language processing deficits, yet the contribution of CNTNAP2 to auditory function remains unknown. We addressed this question with a recently-developed rat model, using the neural measures of hearing sensitivity, auditory responsivity and speed of transmission, and behavioural measures of acoustic reactivity, sensory filtering and sensory-motor gating to allow a broad understanding of auditory system dysfunction across development and the behavioural consequences thereof. The auditory brainstem response (ABR), in vivo electrophysiological recordings from the primary auditory cortex, and manipulation of the acoustic startle response (ASR) were conducted in young (<P42) and adult (>P70) male and female homozygous knockout (Cntnap2-/-), heterozygous knockout (Cntnap2+/-), and wildtype Sprague Dawley rats. Ultimately, we found the knockout rats to have typical hearing sensitivity but reduced neural responsivity in both the brainstem and cortex. Acoustic information was also transmitted slower throughout the brainstem auditory pathway in young Cntnap2-/- rats compared to age-matched wildtype controls; however, this Cntnap2-related delay was no longer present in adulthood. In contrast, the adult auditory cortex revealed a prolonged latency to the response onset and longer response duration. Behaviorally, while a short-term habituation deficit improved with age, the Cntnap2-/- rats displayed a heightened acoustic reactivity and sensory-motor gating deficit when young that worsened with age. To our knowledge, this study represents the first investigation into the role of Cntnap2 in the development of auditory processing impairments which are found in individuals with neurodevelopmental disorders. Overall, these results provide insight into the altered maturation of the different levels of the auditory system and point to potential targets for intervention.

30. Automated motor outcomes in genetic mouse models of neurodevelopmental disorders. Michael C Pride and Jill L. Silverman. MIND Institute and Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, CA 95817. Clinically-relevant outcome measures are required to demonstrate the test utility of innovative drug designs (like gene therapy or stem cells), as well as to validate other traditional medicinal therapies that may be in the drug discovery pipeline by biotechnological and pharmaceutical

companies. However, a major rate-limiting step, is that sophisticated, well-validated, tools that provide precise, translationally relevant (i.e., the same measures in animal models and human patients) outcome parameters are underdeveloped. Our studies utilized automated treadmill walking and pressure sensitive equipment to allow for the collection of a substantial number of quantitative motor parameters such as gait, coordination, stride length, stance width, and pressure of feet (~paws). These innovative quantifiable outcomes revealed 30 metrics of posture, gait and locomotion, stride length, force development, loading, symmetry, and gait variability. Each of these measures are analogous to those being collected by clinics at the MIND Institute, Baylor and UCLA for rare genetic neurodevelopmental disorders characterized by developmental delay and ataxia, such as Angelman and Dup15q Syndromes. Both of these genetic disorders have substantial characteristic motor dysfunction. We collected digital paw prints of each of the four limbs assessed by the Mouse Specifics software. Our studies revealed mutant mice had deficits in numerous parameters on the treadmill assay, as well as in the other more commonly used motor assays. Advantages for our focused study on motor phenotypes resulting from Ube3a overexpression or deletion are the a) strong correlation between motor and social communication abilities, b) motor is highly translatable between preclinical models and human studies, making associated outcome measures extremely useful in a clinical trial, and c) these motor markers could all be used as preclinical screening outcomes for therapeutic development.

31. Nucleus accumbens dopamine modulates social avoidance behavior. Irene Mollinedo-Gajate, Mikel Larranaga, Teresa Sierra, Marta Fernandez, Olga Penagarikano. Department of Pharmacology, University of the Basque Country (UPV/EHU), Leioa 48940, Spain. The mesolimbic dopamine system, composed primarily of dopaminergic neurons in the ventral tegmental area projecting to the nucleus accumbens, has been widely involved in the modulation of rewarding stimuli including positive social interactions. More recent studies have highlighted the role of this system in modulating the response to aversive stimuli as well, including aggressive social interactions. Impaired social behavior is the main hallmark of autism spectrum disorder. This has been proposed to arise from either a reduced motivation to engage in social relationships (i.e. lack of associated salience) or alternatively, to an increased avoidance behavior (i.e. associated negative valence). In this work, we investigated dopamine release in the nucleus accumbens during same sex non-aggressive social interaction, using a genetic mouse model of autism with reported social deficits (Cntnap2-knockout). Eight week animals (wild-type and mutant) were subjected to in vivo freely moving brain microdialysis before, during and after exposure to a non-familiar conspecific of the same sex for 90 seconds. Dopamine concentrations were continuously monitored in the nucleus accumbens and quantified by Ultra Performance Liquid Chromatography coupled with an electrochemical detector. Interestingly, we found that accumbal dopamine basal concentrations in Cntnap2-knockout mice were strikingly lower compared to its wild-type counterparts. Conversely, the short exposure to an unfamiliar conspecific, although significantly increased dopamine concentrations in the nucleus accumbens of both genotypes, it exerted a much more exaggerated effect in mutant than in control mice. This greater change in dopamine concentrations from basal levels observed in mutant mice not unexpectedly was accompanied by increased neuronal activation in the nucleus accumbens as measured by expression of the immediate early gene cFOS. In short, our results suggest that there is an associated high salience driven by social behavior in this model of autism. Future experiments will allow us to determine any potential abnormalities in the encoding of the motivational valence underlying deficits in social interactions in this model.

32. Adolescent Social Isolation in Mice is Associated with Altered Sleep-Wake Behavior and Elevated DeltaFosB Protein Expression. Gongliang Zhang[1], Michael Noback[1,2], Noelle White[1], Spencer Byers[1], Gregory V. Carr[1,2] 1 Lieber Institute for Brain Development, Baltimore, MD 21205, 2 Department of Pharmacology and Molecular Sciences, Johns Hopkins School of Medicine, Baltimore, MD 21205. Social isolation (SI) during adolescence affects neurodevelopment and is a significant risk factor for mental disorders in later life. DeltaFosB is a transcription factor in the Fos family characterized by its accumulation in response to repeated stimulation. Previous studies have demonstrated that chronic stress, drug exposure, natural reward, chronic antidepressant treatment, and

environmental enrichment produce alterations in DeltaFosB expression. In this study, we explored the expression of DeltaFosB in mice that were singly housed from postnatal day 21 to day 35 (SI mice). SI mice display a significant increase in locomotor activity in an open-field arena. SI mice also showed disrupted sleeping patterns measured during 48-hour continuous home-cage behavior analysis. SI mice engaged in shorter and more frequent sleep bouts compared to group-housed littermates. Male SI mice have an increase in DeltaFosB protein level in the medial prefrontal cortex (mPFC), hippocampus, and striatum, but no difference in FosB compared to group-housed littermates. In female mice, the DeltaFosB and FosB protein levels were both elevated in the mFPC, but there were no differences in the hippocampus, or striatum. Immunofluorescent staining also confirmed an increase in DeltaFosB-positive cells in prelimbic and infralimbic areas in the mPFC. Our data suggest that changes in DeltaFosB protein expression may underlie some of the behavioral changes caused by SI in mice.

33. FKBP52 promotes tau aggregation. Criado Marrero, Marangelie[1]; Gebru, Niat[1]; Blackburn, Roy[1]; Smith, Taylor[1]; Vidal, Yamile[1]; Penny, Hannah[1]; Wang, Xinming[2]; Baker, Jeremy[1]; Koren, John; Dickey[1], Chad A.; Blair, Laura J. [1] 1Dept. of Molecular Medicine, Byrd Alzheimer's Res. Inst., Univ. of South Florida, Tampa, FL; 2Dept. of Molecular Pharmacology and Physiology, Univ. of South Florida, Tampa, FL. Tau is a microtubule stabilizing protein that aberrantly accumulates in neurodegenerative diseases known as tauopathies, the most common being Alzheimer's disease. This abnormal tau aggregation contributes to neurotoxicity in the tauopathic brain. Molecular chaperones have been shown to regulate this process. Specifically, the Hsp90 co-chaperone, FK506-binding protein 52 (FKBP52), has been shown to interact with tau and stimulate the production of tau oligomers and fibrils. Since there is evidence that tau aggregation is neurotoxic, we hypothesized that increased expression of FKBP52 in the brain would exacerbate both oligomeric and insoluble tau formation leading to memory impairments a tau transgenic mouse model. To test this, bilateral hippocampal injections of FKBP52 AAV-9 or mCherry AAV-9 (control) were performed in rTg4510 and wild-type mice. After two months of the injections, electrophysiological recordings, hippocampal-dependent memory, and neuronal loss were evaluated in these mice. In addition, we used mammalian cell culture models of tauopathy and primary murine neurons to further characterize the effect of FKBP52 in tau oligomerization and toxicity. Our findings suggest that FKBP52 stimulates tau pathogenesis.

34. Primary progressive dynamic aphasia: a case report. Adithya Chandregowda[1], Joseph Duffy[1], Edythe Strand[1], Mary Machulda[1], Val Lowe[2], Jennifer Whitwell[2], Keith Josephs[1]. 1Department of Neurology-Mayo Clinic, 2Department of Radiology-Mayo Clinic. The semantic, logopenic and agrammatic variants of primary progressive aphasia (PPA) have received considerable attention. We report a case of PPA that was not consistent with any of these well-known variants, but was similar to the entity known as Luria's dynamic aphasia which is characterized by impairment of propositional language, with relatively well-preserved auditory comprehension, grammar, naming and repetition. A 57 year old right handed bilingual (Spanish-English) man presented with an approximately 4 year history of verbal difficulty. A detailed speech and language assessment revealed a disparity between the difficulty he had with discourse formulation and the extent of subareas of language that were intact. An MRI revealed moderately severe asymmetric atrophy of the left frontal lobe and asymmetric focal atrophy within the left perisylvian region. A fluorodeoxyglucose (FDG) PET scan revealed marked hypometabolism in the left lateral frontal lobe, most pronounced in the posterior portion; and in the left anterior cingulate gyrus. Assessment approximately 1½ years later revealed that his verbal difficulty had increased in severity, but the main features continued to be consistent with dynamic aphasia. By presenting results from detailed speech and language, neurological, neuropsychological and neuroimaging testing from his two visits, this study contributes to the understanding of the lesser known primary progressive dynamic aphasia.

35. COMTval158met polymorphism-modulated response to LPS is regulated through dopamine D1 signaling pathway: a first study linking COMTval158met polymorphism and immune mechanisms. J Deslauriers[1,2], X Zhou[1,2], VB Risbrough[1,2] 1 Department of Psychiatry, University of California San Diego, La Jolla, CA; 2 Veterans

Affairs Center of Excellence for Stress and Mental Health, La Jolla, CA. Background: The catechol-O-methyltransferase (COMT) enzyme is implicated in the catabolism of dopamine and plays a key role in cortical signaling. The val158met single nucleotide polymorphism in the COMT gene has been associated with a greater risk of posttraumatic stress disorder (PTSD). In a "humanized" COMT mouse line, male Val/Val carriers, compared to Met/Met carriers, exhibited enduring inflammatory and anxiety-like responses to trauma exposure. Similar effects were found following a severe immune challenge, suggesting a role of COMTval158met-modulated inflammation in stress-induced behaviors. However, the mechanisms underlying the COMTval158met and its contributions to immune function and to trauma-induced inflammation remain unclear. Based on a previous study reporting dopamine D1 receptor-moderated systemic inflammation, we hypothesized that D1 signaling pathway regulates the COMTval158met-modulated response to immune challenge. Methods: The toll-like receptor 4 agonist lipopolysaccharide (LPS; 1 mg/kg, IP) or saline was administered in male Met/Met or Val/Val carriers to induce immune challenge. Simultaneously with LPS treatment and again for two following days, dopamine D1 agonist SKF-82958 (1 mg/kg/day, IP) was administered. One week, enduring anxiety-like behaviors were assessed in the open field and light/dark box tests. A composite avoidance score (Z score) across both tests was calculated for each animal. Results: Val/Val, compared to Met/Met, carriers showed the greatest increase of anxiety-like behaviors following LPS treatment. The D1 agonist SKF-82958 prevented the immune-induced behaviors only in Val/Val mice. Conclusions: These results indicate that dopamine D1-regulated immune pathways play a role in the COMTval158met-modulated response to immune challenge. Taken together with our previous data, these findings indicate that altered dopamine signaling underlie the alterations in immune and behavioral responses to trauma in COMTval158met carriers. Future work will examine the sex-dependent immune mechanisms related to COMTval158met and their modulation by the D1 signaling pathway.

36. Musical pleasure affects forward gait in patients with Parkinson's disease. K. Shin Park[1], Chris J. Hass[1], Bhavana Patel2, and Christopher M. Janelle[1] 1Department of Applied Physiology and Kinesiology, University of Florida 2Movement Disorders and Neurorestoration Center, University of Florida. Neurologic music therapy (NMT) has demonstrated clinical benefits in patients with Parkinson's disease (PD), especially improvement in gait disturbance. Most NMTs use an isochronous metronome pulse called rhythmic auditory stimulation (RAS) which ignores emotional and motivational benefits of music. Given that musical pleasure is associated with activation of the limbic-motor system, pleasurable music may produce beneficial alterations of gait compared to an isochronous beat. We sought to investigate how musical pleasure influences gait function in people with PD. Twelve individuals with mild to moderate level of idiopathic PD (age M = 69.5, SD = 4.96; 2 females; H&Y stage 1 – 3, on-med) completed 2-min walking trials while listening to emotionally-neutral (isochronous beat), self-chosen pleasant (favorite), and experimenter-chosen pleasant (novel) music selections, which were compared with walking at a natural pace (baseline). The tempo of all music selections was matched to the individual walking cadences measured during the baseline trial. The Ambulatory Parkinson's Disease Monitoring system (128Hz, APDM Inc.) was used to record and analyze participants' stride and arm swing characteristics. Favorite music led to faster gait velocity (1.17 ± .04m/s) compared to baseline (1.11 ± .05, $p < .01$) and beat conditions (1.12 ± .04, $p < .01$). The increased velocity was largely driven by longer stride length (1.26 ± .05m) compared to baseline (1.20 ± .05, $p < .01$) and beat (1.21±.05, $p < .01$). Arm swing peak velocity was greater during favorite (235.11 ± 35.08degree/s, $p < .05$) and novel music conditions (238.32 ± 42.28, $p < .05$) compared to baseline (194.75 ± 31.30). Arm swing range of motion (ROM) was greater during favorite (54.18 ± 7.34degree, $p < .01$) and novel music conditions (52.02 ± 7.44, $p < .01$) compared to baseline (44.38 ± 6.89). While novel music increased the variability of stride time (2.36±.18CV%, $p < .05$) and stride length (2.99±.21CV%, $p < .05$) compared to baseline (1.85±.11 and 2.40±.14), favorite music reduced arm swing ROM variability (13.41±1.24CV%, $p < .05$) relative to baseline (18.04 ± 2.76). Findings indicate that pleasurable music may have greater benefits for the improvement of gait amplitude and variability in patients with PD than an isochronous RAS, implying the potential role of the limbic-motor system in restoring and/or compensating for the impaired nigrostriatal pathway in PD.

37. Relationship between the risk of mental health disorders and life habits: a cohort study. Y Mashio[1], T Yoshizaki[2], and H Kawaguchi[1] 1Graduate School of Life Sciences, Toyo University, Itakura Gunma 2Department of Food and Nutritional Sciences, Toyo University, Itakura, Gunma. Recently, the number of patients with mental health disorders has been increasing. Our previous study revealed that we may be able to predict the risk of mental health disorders by analyzing the temporal information of handwriting using a digital pen. The relationship between the risk of mental health disorders and life habits was investigated to confirm this risk predictability and establish a feasible coping strategy at an individual level in a high-risk group. In total, 108 students (age: 18–21 years) were recruited for a follow-up cohort study conducted over 2 years. The participants voluntarily completed the Uchida–Kraepelin test, DIHAL.2, and BDHQ questionnaires. Time intervals between the first and second number stroke (4, 5, and 7; mean time interval: t1) and those between the completion of a number and initiation of the next number (mean time interval: t2) were analyzed. The participants were first classified into two groups according to the mean time interval ratio (t2/t1) observed each year; one group included participants with a t2/t1 ratio ≥ 10 (high-risk group, n = 7), whereas the other group included those with a t2/t1 ratio < 10 (low-risk group, n = 101). The participants were then categorized into two groups according to the change in their mental health risk: one group included participants who moved from the low-risk to high-risk group from year 1 to 2 (worsening group, n = 5), whereas the other group included those who stayed in the low-risk group (healthy group, n = 96). Participant characteristics and questionnaire scores from year 1 were used to analyze differences between the worsening and healthy groups. We also evaluated predictors for shifting from the low-risk to high-risk group using multiple logistic regression analysis. Significant differences were observed in exercise habit and rest habit scores and intake of eicosadienoic acid in year 1 ($p < 0.05$). In addition, the worsening shift was associated with the exercise behavior/condition and eicosadienoic acid intake ratio in year 1 (OR = 0.33, OR = 1.24, $p < 0.05$). These findings suggest that interventions including regular exercise and reduced dietary eicosadienoic acid intake may improve mental health conditions.

38. Deficits in relational memory in the scPCP mouse model for schizophrenia. Margarida Trigo[1], Dr. Jill Silverman[2], Prof. Joanna Neill[1] and Dr. John Gigg[1] 1Faculty of Biology, Medicine and Health, University of Manchester, Manchester, M13 9PT, UK; 2UC Davis Mind Institute, 4625 2nd Avenue, Sacramento, CA 95817, USA. To help develop novel treatments for cognitive deficits in schizophrenia (SZ), the evaluation of novel compounds in SZ models by methods with high translational value to the clinic is required. The Bussey-Saksida touchscreen chamber provides such a translational method, as the touchscreen interface is analogous to that employed in SZ patients. An important cognitive deficit in SZ patients is in relational memory, with patients showing impaired capacity for transitive inference. The transitive inference (TI) task measures subjects' ability to make an indirect logical deduction after learning multiple overlapping discriminations between pairs of images in which one image is rewarded over the other. However, until now, transitive inference has not been tested in models for SZ using the touchscreen operant chamber. Here, we tested for TI deficits in the scPCP mouse model of SZ, which displays both the negative symptoms and cognitive dysfunction phenotypes of SZ. First, we determined whether there was a sex difference in acquiring and performing touchscreen operant behaviour (visual discrimination, reversal and recall) and novel object recognition (NOR) memory in naïve c57BL/6J mice. Male and female mice performed similarly in operant tasks, however, interestingly female mice displayed stronger NOR performance. We, therefore, used female c57BL/6J mice in further experiments. Female mice were trained to criterion (75% correct) on overlapping premise pairs (A > B, B > C, etc.) to establish a reward hierarchy (A>B>C>D>E). Mice were then subject to PCP or vehicle (8 vehicle and 8 controls; 2 10ml/mg/Kg injections per day for 7 days). Cognitive effects of scPCP phenotype were tested by assessing NOR memory. All mice were then tested on novel pairs that either required transitivity (B vs D) or not (A vs E). Final results and analyses of the scPCP protocol on TI will be presented. This is the first report of acquisition and performance gender differences in the touchscreen chambers and also of deficits in transitive inference in the scPCP model, leading to a new view on the need to use both genders when testing in this manner and to the determination of a new deficit in the scPCP model, present in patients, useful when testing for new treatments.

39. Role of neuroinflammation and amyloid in cognitive impairment in a mouse model of Alzheimer's disease. Shenghua Zhu1,2, Jun-Feng Wang1,2, Xin-Min Li3 1 Department of Pharmacology and Therapeutics, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, 2 Kleysen Institute for Advanced Medicine, Health Sciences Centre, Winnipeg, MB, Canada, 3 Department of Psychiatry, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada. In Alzheimer's disease (AD), both amyloid deposition and neuroinflammation appear in the early course and become notably conspicuous as disease progresses. However, the progression of neuroinflammation and its relationship with amyloid deposition and behavioural changes have not been characterized as many underlying mechanisms rarely occur in isolation. Methods: The present study will thoroughly characterize the behaviour of the APP/PS1 mouse model of AD, using a comprehensive test battery designed to assess a variety of behaviours. Using a crosssectional design, these behaviours will be assessed in mice at different ages. Brain pathology measures for amyloid deposition and neuroinflammation are done post-mortem. Results: APP/PS1 mice exhibited significant learning deficits from the age of 5 month, which were aggravated at the later stages of life. However, the degree of memory impairment plateaus after 12 months. Histological analyses showed that an early appearance of amyloid plaques at 3 months of age with a linear progressive increase up to 22 months. This pronounced amyloid deposition was accompanied by a steady increase of the glial fibrillary acidic protein (GFAP) positive astrocytes and CD11b positive microglia up to the age of 9-12 months. Interestingly the expression levels of GFAP rose steeply from the age of 5 months to the age of 9 months and then stabilized at the age of 12 months which coincided with the observed pattern of learning deficits in APP/PS1 mice. Conclusions: These findings provided evidence that neuroinflammation might be involved in the development and progression of cognitive deficits in APP/PS1 mice, suggesting novel intervention and prevention strategies for AD.

40. Effects of experimental concussion by closed head injury on conditioned fear in rats. Melissa Rivera-López, M.A. and Demetrio Sierra-Mercado, PhD. Department of Anatomy & Neurobiology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico 00936. Traumatic brain injury (TBI) affects 4 million civilians and soldiers each year, many of who are diagnosed post-injury with neurological and cognitive dysfunction, such as excess fear. There are common mechanisms that contribute to the neurobiology of TBI and cognitive dysfunction. Notably, both can result in impaired learning and emotional regulation. Although epidemiological studies show a correlation between sustaining TBI and developing excess fear, animal studies show conflicting results. To evaluate the potential relationship between TBI and cognitive dysfunction, a biological link must be examined using reliable injury models and behavioral tests. We are testing the hypothesis that TBI would impair fear learned by Pavlovian conditioning in rats. Clinically, the most common type of TBI is concussion, in which an impact to the head plus angular acceleration produces neurological deficits and cognitive dysfunction. There are homologous brain regions in rodents and humans needed for the expression of fear memories. Dysfunction in the amygdala, hippocampus, and the medial prefrontal cortex (mPFC) underlie deficits in both rodents and humans with fear disorders. Notably, the effects of TBI to activity in homologous brain regions in the rodent are unclear. To address this knowledge gap, we will mimic concussion in rodents using closed head injury (CHI) and sham injury. After recovery, we achieve delay conditioning by pairing an auditory stimulus (e.g. tone) with a foot shock, followed by subsequent tests for memory. Our preliminary results demonstrate that non-injured rats acquire a tone-shock association and express fear as indexed by a lack of movement save those related to breathing, known as freezing. To mimic the scenarios in which TBI occurs prior to or after exposure to an aversive event, we are assessing the delivery of CHI at one of two time points: 1) prior to fear conditioning, or 2) after conditioning. We aim to determine how CHI influences fear and assess activity in homologous brain regions in the rat. This work may lead to novel approaches for understanding and treatment of patients with TBI and fear disorders.

41. Let's get physical: the synergistic effects of exercise and environmental enrichment on behavioral and physiological plasticity in Long-Evans rats. Granger, Megan; Perdomo-Trejo, Jose; Scarola, Samantha; Gerecke, Kim; Bardi, Massimo – Department of Behavioral Neuroscience, Randolph-Macon College, Ashland, VA. Neurodegenerative diseases are most commonly associated with aging, constituting one of the largest threats to the future well-being of our society. Excessive oxidative stress is one of the most dangerous contributors to neurodegeneration. Exercise and enriched environments distinctly have shown to decrease oxidative stress, thus contributing to a delay in cognitive deficits. The main aim of the current study was to investigate the synergic effects of exercise and environmental enrichment on the cognitive and emotional regulation of Long Evans rats (n=28). Subjects were randomly assigned to one of three different groups for two months: control group (NS), standard cage with access to exercise (ES), or enriched cage with access to exercise (EE). Standard housing consisted of a standard laboratory cage (22x43.5x20.5) with corncob bedding. Enriched housing consisted of a much larger cage (61x61x42) containing various natural objects, such as logs, sticks, tree stumps, rocks, halved coconuts, or shells. All animals were housed in pairs. ES and EE groups were allowed the opportunity to exercise (voluntary exercise) 2-3 hours a week in large exercise wheels. After six weeks of exposure, subjects were challenged in the forced swim task (FST) and the persistence task (PT) to establish their physiological and behavioral responses to stress. Corticosterone (CORT) and dehydroepiandrosterone (DHEA) were extracted from fecal samples. ES rats used their wheels significantly more than EE rats ($p=0.011$), and at the same time they interacted with each other significantly less ($p=0.001$). During the FST, EE rats showed the highest levels of DHEA in relation to CORT, an indication of physiological resilience ($p=0.001$; $h2=0.302$). The same group performed better during the PT ($p=0.001$; $h2=0.298$). These preliminary results indicated that the combination of environmental enrichment and exercise can increase cognitive and emotional regulation. Subsequently, rats in the EE group were allowed to exercise for additional six months to assess the long-term consequences of the ES and EE synergic interactions. Preliminary results indicated that the synergic effect of environmental enrichment and exercise had even a stronger effect on the emotional regulations of rats after that time ($p=0.001$; $h2=0.566$), thus confirming the benefits of long-term enhanced physical and environmental stimuli.

42. Locomotor Behavior, Hindlimb Tendon Properties, and Epigenetic Activity in the Spinal Cord of Developing Rats. A. L. Bozeman[1], L. R. Kollmeyer[1], N. Burgett1, J. J. Becker[2], S. K. Funk[1], A. R. Raveling[1], N. R. Schiele[1], T. S. Doherty[3], T. L. Roth[3], and M. R. Brumley[1]. 1Department of Psychology, Idaho State University, Pocatello, ID 83201, 2Department of Engineering, University of Idaho, Moscow, ID 83844, 3Department of Psychological and Brain Sciences, University of Delaware, Newark, DE 19716. The development of motor behavior is a dynamic process that involves changes across multiple levels and systems of the organism. Current research in our lab is examining the relationship among the developing central nervous system, motor behavior, gene activity, and the musculoskeletal system. In the first study, we investigated the relationship between development of the hindlimb Achilles tendon (i.e. collagen structure and mechanical properties) and locomotion (non-, partial, or full-weight bearing) during the early postnatal period. Rat pups were placed in an open-field on postnatal day 1 (P1), 5, and 10. On P10, subjects were euthanized, and hindlimbs were dissected for tendon testing. Behavioral data showed that weight-bearing locomotion increased with age, as expected. Additionally, collagen structure of the Achilles tendon became more organized with age, evident by a more mature "crimping" pattern. The force needed to break the tendon increased almost tenfold from P5 to P10. The second experiment tested rats that received a low-thoracic spinal cord transection or sham operation on P1. On P10, behavioral testing in an open-field occurred, and then subjects were euthanized and hindlimbs were dissected. Behavioral results showed that sham subjects expressed significantly more weight-bearing locomotion than spinal subjects. For tendon testing, the force needed to break the Achilles tendons of spinal subjects was significantly lower than that of shams. Results from both of these experiments suggest that motor behavior and the musculoskeletal system influence each other during postnatal development. Next, we examined methylation of the Brain-Derived Neurotrophic Factor (BDNF) gene in lumbar spinal cord tissue. For this experiment, rats received a spinal transection on P1. On P5 and P10, subjects were euthanized, and spinal cords were extracted for methylation analysis. Results showed

more BDNF methylation in spinal subjects compared to shams; however, there were no differences with age. Together, these studies suggest that a change in one system during development leads to a cascade of changes across systems/levels of analysis. Investigating motor behavior in immature rats is a fruitful model for revealing the nature and mechanisms of developmental interactions.

43. The modulatory effect of rosmarinic acid in the rhythmic motor patterns of the lumbar spinal cord of neonatal mice. Mendez, Laura[1,4]; De Jesus, Kevin[2,4]; Garcia, Andrea[3,4]; Diaz, Manuel[1,4.] 1Department of Anatomy and Neurobiology, University of Puerto Rico, Medical Science Campus. 2Department Biology Science and Math, Interamericana University of Puerto Rico, Bayamon Campus. 3Department Biology, University of Puerto Rico, Bayamon Campus. 4Institute of Neurobiology, University of Puerto Rico, Medical Science Campus. Rosemary (Rosmarinus officinalis L.) is one of the most common household herbs, used as spices in a variety of foods, and employed in traditional medicine for its healing properties. Rosemary is a rich source of active antioxidant constituents such as phenolic diterpenes, flavonoids and phenolic acids. Caffeic acid and rosmarinic acid are its most important bioactive constituents. Rosmarinic acid is one of the most important and well known natural antioxidant compounds, which possesses neuroprotective effects in different models of neuroinflammation, neurodegeneration, as well as chemically-induced neurotoxicity and oxidative stress. These effects are beneficial for cancer patients, patients who suffered a spinal cord injury and for the potential treatment of other neurodegenerative diseases. Nevertheless, it has not been found or determined it this compound produces secondary effects in motor behaviors such as locomotion. Thus, we focused this study in assessing the effects of Rosmarinic Acid as a potential modulator of motor activity using the lumbar spinal cord of neonatal mice which possess the neural network controlling locomotion. The evaluation of this potential modulatory effect was performed through electrophysiological techniques which included extracellular recordings of ventral nerves during a motor rhythm which can be elicited by the application of a mixture of serotonin (5-HT), NDMA (a glutamate analog) and dopamine. We measured changes in the peak amplitude, burst duration and cycle period of the recorded motoneuron-produced rhythm before, during and after the application of Rosmarinic acid at concentrations of 1µM and 100µM. So far, we have not observed significant changes in any of the parameters measured at low (1µM) or moderate concentrations (100uM). These results suggest that Rosmarinic Acid does not alter locomotor activity at these concentrations. Further experiments at higher concentrations will be conducted to assess any effects. These findings support the use of this compound or of the Rosemary plant as part of commercial drugs or natural supplements as possible neuroprotective agents.

44. Protein synthesis is necessary for rapid, estradiol-facilitated social recognition in female mice Paul A. S. Sheppard1, Hayley A. Asling2, Sabrina E.M. Armstrong1, Vissy M. Elad3,4, Daniella A. Vellone1, & Elena Choleris1 [1]Department of Psychology and Neuroscience Program, University of Guelph, [2]Department of Molecular and Cellular Biology, University of Guelph, [3]Department of Human Health and Nutrition Sciences, University of Guelph, [4]Department of Biomedical Sciences, University of Guelph. Estrogens can rapidly facilitate social recognition ¬– the ability of an animal to recognize another. In ovariectomized female mice, social recognition was facilitated within 40 minutes of systemic (Phan et al., 2012) or dorsal hippocampal (Phan et al., 2015) administration of 17β-estradiol (E2). Within the same timeframe, E2 increases dendritic spine density in CA1 dorsal hippocampal neurons (Phan et al., 2012; 2015). Akt pathway-dependent translation of dendritic spine scaffolding protein PSD-95 occurs within 1 hour of estrogen treatment in cultured NG108-15 neurons without a concurrent increase in PSD-95 mRNA, suggesting a key role for translation of the protein from localized mRNA (Akama & McEwen, 2003). In primary cultured hippocampal neurons, ERK pathway-dependent translation of dendrite-localized mRNA occurs within 30 minutes of E2 treatment (Sarkar et al., 2010). Although we found dorsal hippocampal activation of both the ERK and Akt pathways is necessary for the rapid facilitation of social recognition by E2 in ovariectomized female mice (Sheppard et al., 2016; 2017), the necessity of protein synthesis to this effect has not yet been examined. Here we first determined the highest doses of protein synthesis inhibitor anisomycin that does not block social

recognition when infused in the dorsal hippocampus of ovariectomized female mice 15 min prior to testing. We then determined whether this dose of anisomycin could prevent the enhancing effects of E2 (as in Phan et al., 2015) in a task where control mice do not typically perform social recognition. These paradigms consist of habituation trails where two female conspecifics are presented and one test trial where one conspecific is novel and the other is familiar. The paradigms are completed within 40 minutes of E2 administration, thus enabling investigation of rapid effects of estrogens. Protein synthesis was found to be necessary for E2 to rapidly facilitate social recognition as a dose of 4μg/hemisphere of anisomycin blocked the facilitation of social recognition by E2. A follow-up is currently underway to determine whether transcription is necessary for social recognition. These studies will provide a mechanism through which estrogens rapidly facilitate social recognition.

45. Investigation of the Social Neuroscience of Human Animal Interactions. Wendy L. Wilson[1], Kendra Cox[1], Cade Coles1[1], Tyrel Brown[1], Kacy Waldner[1], Shelby Gustafson[1]. [1]Dickinson State University. Human-animal interaction (HAI) has been an area of interest for centuries, with some of the first records showing calming effects in the presence of a canine. Several hormones and physiological processes are involved in mediating social interactions of bonding and attachment in human and companion animals. Oxytocin is believed to regulate several behaviors associated with positive HAI's in human-animal dyads, with the majority of research in human-canine dyads. A relatively new area of research, understanding the biological underpinnings of the beneficial effects of human-equine dyads has surfaced due to both anecdotal reports of stress relief in horse owners and the current rise in equine assisted therapies (EATs) and EAT facilities around the world. Animal-assisted therapy has been in existence with canines for several decades, however, EAT has only recently gained momentum. Several hormones have been a point of interest for researchers such as oxytocin vasopressin, cortisol, and progesterone. These hormones appear to work in conjunction to produce behaviors associated with HAI's and associated positive effects of these interactions. Progesterone, has been linked with anxiolytic, mood-lifting, calming and positive psychological effects in bonding and attachment situations. In contrast, low levels of cortisol have been associated with oxytocin release and decreased stress levels. Due to current limited validity of salivary oxytocin assays, salivary levels of progesterone and cortisol will be collected and analyzed in this study. In addition, physiological and subjective psychological measurements will be investigated including heart rate of both horse and human in addition to a bonding scale adapted for equine-human dyads. Baseline samples will be taken from human and equine pairs followed by a thirty-minute interaction session. After interaction post-test samples will be collected from each pair, followed by the attachment & bonding scale. Expected results: biological and physiological measurements will correlate with attachment and bonding scale values in humans, with higher progesterone levels, lower heart rates, and decreased cortisol levels following the interaction session compared to baseline levels in human-equine pairs.

46. Role of M1 and M2 muscarinic acetylcholine receptors in social learning in female mice. Kelsy Ervin, Sarah Howard, Cecil Dana Main, Elena Choleris. Dept. of Psychology, University of Guelph, Guelph, ON N1G 2W1 Canada. Social learning is a learning strategy in which animals learn by observing or interacting with another animal, rather than individual trial-and-error learning. Though prevalent in humans and many animal species, social learning is understudied compared with individual learning and hence we know little about its specific neurobiological mechanisms. Social learning can be tested in laboratory rodents with the social transmission of food preferences (STFP), in which an observer animal prefers to eat a novel food it previously smelled on the breath of a demonstrator over other equally unfamiliar foods. In male rats, muscarinic acetylcholine receptor (mAChR) signaling plays a major role in the acquisition of a socially learned food preference (Boix-Trelis et al, 2007, Neurobiol Learn Mem, 87:659; Carballo-Márquez et al, 2009, Hippocampus, 19:446; Carballo-Márquez et al, 2009, Neurobiol Learn Mem, 91:98). We found that mAChR signaling is also necessary for social learning in the STFP in female mice. Female observer mice, either gonadally intact or ovariectomized, were impaired in the STFP when treated with the mAChR antagonist scopolamine before interaction with a demonstrator. Scopolamine blocked social learning when mice were tested for food preference immediately and after a 48h

delay, suggesting that mAChRs are involved in acquisition and possibly consolidation of socially acquired information in the STFP. To determine which specific mAChR subtypes are involved, we are testing the effects of the M1 receptor antagonist dicyclomine and the M2 receptor antagonist AF-DX 116 on social learning in the STFP. Female observer mice receive 1, 4, or 8mg/kg dicyclomine or 0.3, 1, 3, or 6mg/kg AF-DX 116 30min prior to interaction with the demonstrator. Observer mice are tested for a food preference 48h later. Given the known involvement of both M1 and M2 receptors in learning and memory (Bubser et al, 2012, Muscarinic Receptors, ed. Fryer et al; Carruthers et al, 2015, Neurosci Biobehav R, 55:393), we predict that treatment with dicyclomine and AF-DX 116 will block social learning. These investigations will lead us toward a clearer view of cholinergic mechanisms underlying social learning, an important learning strategy for humans and many other animals. Funded by NSERC.

47. Prior experience, an orexin 2 receptor agonist, and cEPo promote anxiolytic behaviors. Jazmine DW Yaeger[1,2,3,] Clarissa D Staton[1,2,3,] Samuel Sathyanesan[2,3], Cliff H Summers[1,2,3] 1Department of Biology, University of South Dakota, Vermillion, SD 57069 USA; 2Neuroscience Group, Division of Basic Biomedical Sciences, Sanford School of Medicine. University of South Dakota, Vermillion, SD 57069 USA; 3Veterans Affairs Research Service, Sioux Falls VA Health Care System, Sioux Falls, SD 57105 USA. The exact relationship between motivated, learned, and fear responses remains highly elusive despite the dynamic interconnected nature of each component during a stressful situation. The hypothalamic-generated orexins (OrxA and OrxB) are important for the modulation of drive, decision-making, and arousal. These neuropeptides are modified in concert with neurotrophins, like brain-derived neurotrophic factor (BDNF), during episodes of social stress. While changes in BDNF are linked to fear learning and the phenotypic expression of anxious and depressive behaviors, a parallel role may be associated with erythropoietin (EPo). The Stress Alternatives Model (SAM) is a modified social defeat paradigm, in which a smaller mouse is provided an opportunity to escape from a larger aggressive mouse or remain submissively in the arena. Throughout four days of SAM interaction, a mouse must execute decision-making in a fear-provoking environment. In this way, the SAM incorporates aspects of motivational states with learning in stressful situations. We demonstrated that the anxiolytic (Escape) and anxiogenic (Stay) phenotypes derived from the SAM can be partially manipulated through prior exposure to the escape route. Furthermore, animals expressing the escape phenotype, regardless of escape experience, displayed a resilient response to the Social Interaction/Preference (SIP) Test when compared to their non-escaping counterparts. Targeting whole brain orexin 2 receptors (Orx2) with the antagonist MK-1064 reversed escape behavior by 50% in the SAM and diminished resilient responses in the SIP Test; whereas, mice treated with a vehicle did not change. Alternatively, the Orx2 agonist [Ala11,D-Leu15]-Orexin B increased resilient expression in non-escaping mice. Treatment with intracerebroventricular (icv) infusions of carbamoylated EPo (cEPo) reversed 30% of anxiogenic responses (Stay to Escape) in the SAM arena. In addition, cEPo promoted nearly 100% resiliency, regardless of phenotype, in the SIP Test. Together, these results demonstrate the expression of anxious behaviors requires modulation of learning, motivation, and fear. While each plays a unique role during anxiogenic responses, all contribute to the formation of anxious phenotypes.

48. Stress Resilience: A State of Mind, A State of Gut. Anand Gururajan[1,2], Ana Paula Ventura-Silva[2], Josh Lyt[2], Thorsten Becker[2], Marcel van de Wouw[2], Marcus Boehme[2], Barbara Merckx[1], Niamh Wiley[3], Gerard M Moloney[1,2], Catherine Stanton[3], Ted G Dinan[2,4], John F Cryan[1,2] 1Department of Anatomy & Neuroscience, University College Cork, Ireland, 2APC Microbiome Institute Science, University College Cork, Ireland, 3Food Biosciences Department, Teagasc Food Research Centre, 4Department of Psychiatry & Neurobehavioural, University College Cork, Ireland. Background: The perception of stress exposure varies between individuals and depends on whether they are stress-resilient or stress-susceptible. These divergent phenotypes are underscored by a variety of central and peripheral physiological processes. The aim of our study was to identify these processes using a chronic stress paradigm in mice. In particular, we analysed gene expression in the bed nucleus of the stria terminalis (BNST), a relatively understudied structure in this context, and examined the faecal

microbiome as a predictor of response to the stress paradigm. Methods: Male C57Bl/6 mice were subjected to chronic psychosocial defeat stress after which they were tested for social avoidance behaviour to classify mice as being either resilient or susceptible. The day before the first and the day after the last defeat session, tail blood samples were collected for analysis of plasma corticosterone and faecal samples were collected for 16S-rRNA sequencing. Mice were culled the day after behavioural testing. The BNST was dissected out from brains and RNA was extracted for sequencing. Results: Peripheral corticosterone levels were higher in stress-susceptible than stress-resilient mice after the social defeat stress paradigm. At baseline, the relative abundance of the specific families of gut microbes was higher in stress-susceptible than stress-resilient mice. RNA-seq analysis of the BNST revealed differential expression of several genes between groups. Furthermore, in resilient mice we observed increased expression of Pac1r, a receptor for pituitary adenylate cyclase activating peptide which has previously been implicated in the response to chronic stressors. Conclusions: Consistent with recent literature, we have shown that stress resilience is defined by a complex molecular and physiological profile which spans central and peripheral compartments. Our faecal microbiome data indicates that gut bacteria may be a predictive biomarker of stress response and that the upregulation of Pac1r in the BNST is a neuromolecular mechanism which is critical for the development of stress resilience.

49. Managing threat-reward conflict: strategies of conflict-based decision making. Hector Bravo-Rivera[1], Patricia Rubio-Arzola[1], Paula Rodriguez-Aquino[3], Albit Caban-Murillo[4] and Gregory J. Quirk[2]. Depts. of Psychiatry 2 and Anatomy & Neurobiology 1, Univ. of Puerto Rico School of Medicine, San Juan, PR 00936 2, Dept. of Biology, Univ. Of Puerto Rico, Bayamon, PR 009593, Univ. of Puerto Rico Rio Piedras, San Juan, PR 009364. The pursuit of reward and avoidance are two major behavioral motivators. Failure to balance these motivators results in maladaptive behaviors and may underlie many pathological conditions. Many studies focused on the neural substrate of avoidance, as well as reward seeking. However, little is known about the interaction between avoidance and reward-seeking circuits that result in adaptive behaviors. Previous work from our group has shown that rats learn to avoid foot-shocks by stepping onto a nearby platform when they hear a 30s tone that co-terminates with a 2s shock (Bravo-Rivera et al., 2014). In the platform-mediated avoidance task, rats continually press a lever to receive a reward pellet delivered on a variable interval schedule. Avoidance comes at a cost because the food lever cannot be reached from the platform. This cost is minimal, because food is also available during the inter-tone intervals. We modified the task to increase conflict by limiting food availability to the tone period. A light indicating food availability turned on at the same time as the tone-predicting shock. We observed three different behavioral responses to this conflicting situation. 10% (8/77) rats spent all the time on the platform and never pressed for food (avoidance-preferring subgroup). This lack of food seeking can be interpreted as the cost of excessive avoidance, and is not optimal. Finally, the remaining 18% (14/77) rats engaged in excessive food seeking showing little to no avoidance (food preferring subgroup). The increased number of footshocks received by the food-preferring group is the cost of excessive food seeking and is not optimal. In contrast, 72% (55/77) rats were able to accommodate both food seeking and avoidance behaviors, by timing the occurrence of the shock (timer subgroup). Because the shock occurs 28s into the tone-light stimulus, these rats increased their food seeking during the early portion of the tone and avoided more as the tone progressed. Together, these findings revealed different naturally-occurring sub- groups, characterized by their contrasting behavioral response to threat-reward conflict. The approach of focusing on naturally occurring behavioral differences may provide insight into the circuits that drive decision making and their potential dysfunction in anxiety or addiction related disorders.

50. What the health? Investigating the immunomodulatory effects of stress and environmental enrichment in Long-Evans rats. Scarola, Samantha; Perdomo-Trejo, Jose; Granger, Megan; Gerecke, Kim; Bardi, Massimo – Department of Behavioral Neuroscience, Randolph-Macon College, Ashland, VA. Stress can influence the secretion of neuroendocrine mediators, thereby exposing cells of the immune system to an altered cross-talk. The current study aimed to investigate the long-term synergic effect of stress and environmental enrichment

sessions on the immune response of Long-Evans rats. Subjects (n=38) were assigned to four treatment groups: (1) chronic stress, environmental enrichment, (2) acute stress, environmental enrichment, (3) chronic stress, no enrichment and (4) acute stress, no enrichment. Rats exposed to enrichment were placed in an open-field enclosure filled with objects in different areas (playing, hiding, and climbing) for just 30 minutes every other day, thus modeling the effects of a temporary increase in environmental stimuli. Animals assigned to chronic stress groups were exposed to predator sound stressors for 30 minutes daily, while animals assigned to acute stress groups were exposed only once a week for 30 minutes. After seven weeks of treatments, rats were challenged with the forced swim test. Biological samples were collected to measure corticosterone (CORT), dehydroepiandrosterone (DHEA), oxytocin (OT), testosterone (T) and cytokines IL-6 and IL-10. Results suggested that rats exposed to chronic stress exhibited more depressive symptoms. Additionally, rats exposed to chronic stress had a lower DHEA/CORT ratio, suggesting an increased allostatic load. Enrichment exposure showed to be a modulator of these negative effects of chronic stress, lowering overall CORT and T levels and increasing DHEA and OT levels in animals exposed to the predator sound. The immune response was impaired in rats exposed to chronic stress, but the effect of environmental enrichment helped to mitigate the cross-talk with cells producing IL-6. More importantly, the combination of acute stress and exposure to an enriched environment returned the healthier profile both in terms of immune activation and stress regulation. Using a Multi-Dimensional Scaling (MDS) model, we found that a combination of 'good' stress and exposure to brief sessions of enriching stimuli can reliably predict health on Long-Evans rats. In the next phase of this study, the neuroimmunological effects of stress and enrichment will be analyzed using IBA-1 immunohistochemistry. Further, cyclin dependent kinase 5 immunohistochemistry will allow for the investigation of the effects of stress toxicity, and BDNF will be used to further investigate the effects of enrichment on resilience.

51. Acute stress response to the "panel-out" TSST protocol among African American and white college students. Jennifer C. Parada[1], Melissa A. Birkett[1]. 1Northern Arizona University. Encounters of racial discrimination can be appraised, cognitively and physiologically, as chronic stressors. Members of racial minority groups experience significantly more race-related discrimination, as well as greater incidence of chronic illnesses (e.g., heart disease, cardiovascular disease, diabetes) compared to white Americans, which are is associated with chronic stress. To date, much is unknown about acute physiological stress responses among healthy African Americans. The present study investigated acute stress response activation to the modified "panel-out" Trier Social Stress Test (TSST) among African American and white college students. Systolic and diastolic blood pressure (BP) measurements were taken before and after the TSST, and participants were asked about their daily and lifetime encounters with racial discrimination. It was hypothesized that compared to white participants, African American participants would experience more daily and lifetime encounters of racial discrimination, and higher systolic BP at baseline and after the TSST. Preliminary results suggest a trend for African American participants (N = 6) to report experiencing more lifetime instances of race-related discrimination compared to white participants (N = 6). Furthermore, African American participants reported experiencing significantly more daily encounters of racial discrimination (M = 16.17, SD = 3.97), compared to white participants (M = 11.17, SD = 2.04), $t(10) = 2.74$, $p = .021$, $d = 1.58$. Although a main effect of systolic BP was found, $F(1, 10) = 48.64$, $p < .001$, $r = 0.12$, there was no BP x race interaction, $F(1, 10) = .14$, $p = .719$, $r = 0.05$. Planned contrasts revealed a significant mean difference between baseline BP (M = 103.00, SE = 3.53) and BP immediately after the TSST (M = 120.25, SE = 3.49). Altogether, the preliminary results suggest that African American college students tend to experience more lifetime race-related discriminatory encounters and significantly more daily racial discrimination than white students. Additionally, the modified "panel-out" TSST significantly increased BP. Our findings on differences in experiences with racial discrimination support existing research on the higher frequency of racial discrimination among racial minority groups, which may be related to negative health outcomes in later life. We also suggest that the "panel-out" manipulation is an effective protocol to induce an acute stress response in laboratory settings.

52. Neural and endocrine correlates of maternal buffering of fear in vulnerable infants. A. M. White[1,2,3,] J. Hider[1,3], Dj. Chang[1,3], R. M. Sullivan[4], H. Akil[1,2,3,] J. Debiec[1,2,3;] 1The Molecular and Behavioral Neuroscience. Institute, 2Neuroscience Graduate Program, 3Deptartment of Psychiatry, University of Michigan, Ann Arbor, MI; 4Emotional Brain Institute, Nathan Kline Institute & New York University School of Medicine, New York, NY. During the early stages of life in altricial species, the caregiver is a potent regulator of the infant's physiological and emotional state. While rat pups can learn to avoid an odor paired with a mild foot shock from the 10th day of life (postnatal day - PND - 10), this learning is abolished when the odor-shock pairing is performed in the presence of a non-fearful dam. This effect is supported by suppressed release of the stress hormone corticosterone (CORT), an effect termed maternal buffering of fear. However, hereditary and experiential factors may alter the vulnerability to early life aversive experiences and the effectiveness of social buffering mechanisms. We have previously shown that Sprague-Dawley (SD) rat pups from a selectively-bred anxious rat phenotype (ANX) are vulnerable to precocious acquisition of fear conditioning and elevated CORT responses to stress. Here, we examine the maternal buffering of fear in ANX rat pups at early infancy (PND 4) and one week after weaning (PND 28). Pups received 11 pairings of an odor conditioned stimulus (CS) and a 1s 0.4 mA tail shock in the presence or absence of an anesthetized dam. Control groups included ANX pups which received 11 odor presentations in the absence of shock. CORT levels were measured before and after fear conditioning. Pups were exposed to the CS 3 times during a freezing test at PND 11 or 29 in order to assess fear memory. Behavior was video recorded and pups' freezing in response to the CS was scored. Maternal presence was able to block fear conditioning in ANX pups conditioned at PND 4 ($p = 0.68$) and at PND 28 ($p = 0.21$). Additionally, maternal presence was also able to block neural activity in the lateral, central and medial amygdala nuclei ($p's < 0.05$). Surprisingly, maternal presence did not block a rise in corticosterone in ANX pups that received odor-shock pairings at PND 4 relative to pups that received exposure to the odor alone ($p = 0.004$). These findings suggest that although ANX pups can acquire fear conditioning and CORT responses to stressors at an earlier age than wild-type SD rats, the presence of the dam continues to serve as a potent regulator of emotional state at older ages than expected. Additionally, it suggests that CORT may not be the sole mechanism through which maternal buffering operates, and opens new avenues for exploring the underlying neurobiology of this phenomenon.

Saturday, June 30

8:00-9:00 **Keynote Speaker: Sex differences in motivation and addiction.**

Becker, Jill B., University of Michigan, Ann Arbor, MI, USA

Sex differences in motivation and addiction. Becker, J B. Department of Psychology and Molecular & Behavioral Neuroscience Institute, University of Michigan, Ann Arbor, MI USA. Females and males make different choices in order to survive and reproduce successfully. Environmental influences interact with biological sex differences during development, and in the adult, to produce and sometimes exacerbate sex differences in the brain. In the female rat, estradiol decreases food intake and the motivation for food while enhancing motivation for a mate or drugs of abuse. Sex differences in the motivation to take drugs of abuse, escalation of drug taking behavior, and the transition to addiction are seen for all classes of abused drugs in humans and rodents. Using the rat as an animal model, we find that in females there are rapid effects of estradiol on the ascending dopamine system that enhance the female's motivation to engage in these behaviors. Female rats exhibit greater behavioral sensitization to cocaine, acquire cocaine self-administration more rapidly, and work harder to receive cocaine than males, and estradiol enhances these sex differences. We find that in rats, vulnerability to addiction can be identified, within the larger population, based on their preference for cocaine over palatable food rewards. These cocaine-preferring rats increase their drug intake at the expense of pellets, displayed greater motivation for cocaine, attenuated motivation for pellets and an attenuated cocaine-induced dopamine release in nucleus accumbens, compared with animals that preferred palatable food pellets. Finally, females are more likely to develop this cocaine preference than are males. Understanding the neural bases for sex differences in motivation and the ways that males and females differ are important for our understanding of the

variety of mechanisms involved in the neural changes associated with sex differences in motivation and addiction. These findings will be discussed within the larger context of sex differences in addiction.

9:30-11:30 **Past-Presidents Symposium: Granularity mismatch in behavioral neuroscience: Do advances in the control of neuronal circuits produce commensurate gains in our understanding of how normal and abnormal behaviors are expressed?** Chair: John Bruno, The Ohio State University; Co-Chair: Kelly Lambert, University of Richmond.

In search of relevant biobehavioral umwelts in preclinical neuroscience investigations: Aligning behavioral and neurobiological approaches in animal models of depression and emotional resilience. Lambert, K., Dept. of Psychology, University of Richmond, VA 23173. Although behavioral approaches contributed by the pioneering 20th century behavioral psychologists provided a welcomed systematic analysis of cognitive, emotional and behavioral responses, the integrative role of neurobiological factors was typically not a priority in early behavioral investigations. Decades later, as neurobiological approaches became more sophisticated, many behavioral techniques remained decontextualized and simplistic. Applied to clinical disorders such as depression, it is imperative that the context- and species-appropriate aspects of ecologically relevant responses are considered when interpreting responses as depressive and/or adaptive/resilient. An evaluation of the forced swim test provides an opportunity to consider the ecological relevance of a popular behavioral task in the context of specific behavioral responses and accompanying neurobiological correlates. As we seek increased synergy between the specificity of behavioral and biological methodological approaches, salient markers of susceptibility and prognosis of various psychiatric illnesses are more likely to be identified---leading to heightened translational value. Additionally, novel approaches to behavioral assessment, as endorsed by the NIMH's Research Domain Criteria (RDoC), will likely generate more pluralistic biobehavioral approaches for disorders such as depression (described by Krakauer et al., 2016). Thus, innovative applications of neurobiological techniques (e.g., neuroepigenetic, chemogenetic, behavioral microsequencing, and sophisticated statistical approaches) will facilitate a greater understanding of the role of relevant neural networks in the emergence of behavioral output characteristic of both adaptive (resilient) and maladaptive (depressive) responses.

Understanding the molecular basis of adaptive environmental interaction with the deep genome in the context of behavioral models of stress related mental disorders. Richard G. Hunter, Ph.D. Department of Psychology, University of Massachusetts Boston and the Rockefeller University. The advent of next generation sequencing technologies (NGS) has transformed the level of breadth and depth with which we can observe the molecular interactions of genome with environment. With regard to behavior and complex mental disorders NGS has forced a move away from simple Mendelian explanations for behavioral variation. In the area of epigenetics it has allowed us to understand how environment can produce lasting, potentially intergenerational changes in susceptibility and resilience without altering the genome. On the other hand it has revealed a genome that is much more complex and dynamic that expected. Rather than being Junk, much of the deep genome appears to be functional, and much of it, notably retrotransposons (RT) are also potentially mobile. A number of lines of evidence now show that RTs are regulated by environmental stressors in ways that could prove either adaptive or maladaptive at the level of both organism and species. Further, these elements show far more variation both between and within species. Thus, the differences between the non-coding deep genome of Chimpanzees and Humans are at least twice the widely reported difference between the coding regions of the two species. In the same vein, it has been estimated that each individual human has at least one "private" RT unique to him or her. We have shown that two specific RT, the B2 SINE and the IAP endogenous retrovirus, appear to be directly regulated by corticosteroids. Further, differences in expression of these elements in the hippocampus are correlated with behavioral coping style. This provides a proof of principle that the activity of the deep genome has consequences for our understanding of behavior and stress related disease.

Convergent neural biomarkers to bridge the species divide in behavioral neuroscience for psychiatric research. Jared W. Young[1,2]*, Savita G. Bhakta[1], Andrew Bismark[1,2], Gregory A. Light[1,2], Neal R Swerdlow[1], James Cavannagh[3], and Jonathan L. Brigman[4] 1 Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804, USA. 2 VISN-22 Mental Illness Research Education and Clinical Center, VA San Diego Healthcare System, San Diego, CA, USA. 3 Department of Psychology, University of New Mexico, 1 University Blvd, Albuquerque NM 87131, USA 4Department of Neurosciences, University of New Mexico School of Medicine, 1 University Blvd, Albuquerque NM 87131, USA. Neuroscience and bioengineering have resulted in increasingly complex and detailed understanding of neural processors. These detailed studies occurring at the cellular level provide remarkable insight into aspects of rodent behavior but limited knowledge of how the brain mediates disease-relevant behavior at the macro level. Electroencephalographic (EEG) biomarkers of behavioral performance are compelling neural-based biomarker of performances for cross-species translation (Featherstone et al, 2015). As such, NIMH called for the development of paradigms to increase translatability from preclinical-to-clinical studies, addressing this critical need for: i) neurophysiological biomarkers of behaviors relevant to domains affected in psychiatric patients; ii) that can be conducted across species; and iii) that are altered by drug treatment. We recently developed a series of behavioral tasks across species for assessing domains of function like cognitive control, effortful motivation, and reward learning. These tasks utilize both behavioral and EEG measurement of performances. These tasks have already proven sensitive to disruption in patients with schizophrenia, with concomitant reflections of EEG deficits. The availability of these tasks in mice provide a greater depth of construct validity for rodent models of domains affected in schizophrenia. Future studies utilizing these assays will also be able to determine whether specific treatments exert consistent effects across species on behavior and neurophysiological biomarkers, providing direct construct validity of function and predictive validity for drugs targeting cognitive dysfunction in psychiatric conditions. The generation of cross-species tasks with a macroscopic viewpoint to a variety of domains of function is critically needed to bridge the species divide and understand the driving neuroscience underlying behavior.

Lessons learned from a behavioral neuroscience approach to the animal modeling of clinical syndromes. John P Bruno[1], Valentina Valentini[1,2], Jackson Schumacher[1], and David Phenis[1] 1Departments of Psychology and Neuroscience, The Ohio State University, Columbus, OH 43210 2Dipartimento di Tossicologia, Universita di Cagliari, Cagliari, Italy. The methodologies for selectively manipulating brain activity at the level of molecules, cell-specific targets, circuits, and distributed neural systems are becoming more and more advanced. At the same time, a similar reductionistic approach to a microanalysis of complex behavioral output has lagged behind. A result of this granularity mismatch in that we continue to gain insights into neuronal activity patterns that appear to be either necessary or sufficient conditions for behavioral output but, it is not clear whether we gain a comparable understanding of the exact processes that give rise to the expression and mediation of complex behaviors. This presentation will highlight research conducted on validating animal models of several clinical syndromes (Parkinson's Disease; Dementia; and Schizophrenia). We will focus on the use of ever-increasingly sophisticated neuronal methods and the challenges associated with further understanding the process of behavioral output. A number of important lessons and discussion topics can be drawn from these research programs, including the following issues: a) are neuronal and behavioral measures collected in the same subjects? b) is there sufficient attention to construct validity of behavioral measures? c) are measurements of neuronal activity conducted under basal and 'activated conditions'? d) are there mismatches in temporal resolution between neural and behavioral outputs and how limiting are these differences? e) is hypothesis testing extended outside of the laboratory?; and f) are cross-species comparisons conducted?

9:30-11:30 **Symposium: Using genetic mouse models to understand the synapse in cognition and disease.** Chair: Elizabeth Manning, University of Pittsburgh. Co-Chair: Jess Nithianantharajah, The Florey Institute of Neuroscience and Mental Health.

Neural activity and deficits in executive control in GluN2B conditional knockout mice. K. Marquardt, J. Kenton and J. L. Brigman. Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM 87131, USA. New Mexico Alcohol Research Center, UNM Health Sciences Center, Albuquerque, NM 87131, USA. N-methyl D-aspartate receptors (NMDAR) are essential for forms of synaptic plasticity that mediate cognitive function. The ratio of GluN2A to GluN2B-containing NMDAR is hypothesized to play a crucial role in the plasticity required to form, and flexibly alter, new associations. Learning across multiple paradigms increases the GluN2A/GluN2B ratio and the threshold for inducing plasticity. The relative expression of GluN2A and GluN2B is therefore thought to determine the induction threshold of plasticity. Importantly, GluN2B is the predominant subunit expressed during development and may be dysregulated in neurodevelopmental disorders. Behavioral studies support the role of GluN2B-containing NMDAR in plasticity and learning with knockdown, age-related loss, or decreased tyrosine phosphorylation of GluN2B impairing hippocampal and cortical plasticity and learning. In contrast, transgenic overexpression or decreased degradation of GluN2B enhances hippocampal LTP and learning. We have previously shown that conditional knockdown of corticohippocampal GluN2B spares discriminative learning, but increases perseverative responding significantly during reversal in multiple modalities. In contrast, loss of GluN2B in the dorsal striatum (dS) broadly impairs associative learning. Acute pharmacological GluN2B antagonism in the orbitofrontal cortex (OFC) or dS recapitulates these effects, increasing perseveration during early reversal or errors during learning respectively. To further elucidate the mechanisms underlying these changes, we utilized in vivo electrophysiology to record neuronal activity and local field potentials (LFP) simultaneously in the OFC and dS of mice with deletion of GluN2B in cortical and hippocampal principal cells performing touchscreen visual reversal learning. Reversal impairment produced by corticohippocampal GluN2B deletion was paralleled by abnormal functional connectivity between the OFC and dS. Specifically, Glun2BNULL mice showed significantly increased and sustained inter-trial phase consistency in the OFC across sessions that was concomitant with increases in the dS. These alterations in corticostriatal coordination were not associated with disruption in firing activity within the OFC itself, but rather altered coordinated activity of both OFC and dS. Analysis of inter-site phase consistency revealed significant reductions in OFC-dS communication during critical periods of early reversal and aberrant increases during later learning stages. Additionally, in a complementary study we found that exposure to alcohol during development led to reduced GluN2B expression in the OFC when measured in peri-adulthood. These data demonstrate highly dynamic patterns of cortical and striatal activity concomitant with reversal learning, and reveal GluN2B as a key molecular mechanism underpinning the timing of these processes.

Using in vivo calcium imaging to study prefrontal cortex contributions to OCD: Investigating reversal learning in the SAPAP3 knockout mouse model. Manning, Elizabeth E[1,2]; Hyde, James[1]; Dombrovski, Alexandre Y[1]; Torregrossa, Mary M[1]; Kass, Robert E[2,3,4]; Ahmari, Susanne E[1] 1Department of Psychiatry, University of Pittsburgh, Pittsburgh, USA. 2Center for Neural Basis of Cognition, Carnegie Mellon University and University of Pittsburgh, Pittsburgh, USA. 3Machine Learning Department, Carnegie Mellon University, Pittsburgh, USA. 4Department of Statistics, Carnegie Mellon University, Pittsburgh, USA. Functional imaging studies have strongly implicated prefrontal cortex (PFC) dysfunction in the pathophysiology of obsessive compulsive disorder (OCD). However, the mechanisms by which this gives rise to OCD symptoms are unclear, with hyperactivity typically observed at baseline and during symptom provocation, and hypoactivity typically observed during cognitive testing (e.g. reversal learning). This raises the question of whether overlapping or distinct populations of neurons contribute to these different patterns of neural activity and associated symptoms. We can now address this question using newly developed miniature microscopes for in vivo calcium imaging in freely moving rodents, which allow neural activity of individual neurons to be compared between different paradigms relevant to the cognitive impairments (i.e operant reversal learning) and symptoms (i.e. compulsive grooming) observed in OCD. We have recently demonstrated that SAPAP3 knockout mice (KOs), which exhibit OCD-relevant compulsive grooming, also show impairments in reversal learning ($p<0.001$). Approximately half of KOs (13/28) are unable to acquire a reversed contingency during 5 days of training, whereas the other half perform similarly to wild-type (WT) littermate controls. Expression of the immediate early gene cFos associated with acquisition of reversal learning on day 1 of training was examined in a separate cohort of mice using general linear mixed-effects models. This revealed unique associations between reversal acquisition in SAPAP3 KOs and cFos expression in the nucleus accumbens, prelimbic PFC and lateral

orbitofrontal cortex, suggesting that compensatory activity in this circuit may support successful reversal in a subset of KOs. Ongoing studies are measuring neural activity in PFC neurons in vivo with miniature microscopes during reversal learning to test this hypothesis more precisely. Activity will be aligned to specific behavioral events during reversal learning (correct/incorrect responses, reward retrieval) and compulsive grooming (initiation and termination of grooming bout), and compared between the two OCD-relevant paradigms. Our studies are among the first to describe cognitive impairments in an OCD-relevant transgenic mouse model, and ongoing studies using in vivo calcium imaging should provide new insight about the specific patterns of neural dysfunction in the PFC associated with compulsive grooming, cognitive impairment and intact cognition relevant to OCD.

Unravelling the role of neuroligins in decision-making. Nithianantharajah, J.[1,2] 1. Department of Florey Neuroscience, University of Melbourne, Australia. 2. The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia. Sensory information from the environment is ultimately processed at the level of synapses, the connection between neurons that form the most fundamental information-processing units in the nervous system. Human genetic studies continue to increasingly highlight that many of the mutations implicated in cognitive disorders converge upon genes associated with the synapse. Neuroligins are a family of postsynaptic cell adhesion molecules that form trans-synaptic complexes critical for synapse specification, function and plasticity. Our recent studies have investigated the role of all four neuroligin (NLGN) gene family members (Nlgn1, Nlgn2, Nlgn3 and Nlgn4) in regulating complex cognition in mice using the rodent touchscreen assays. Our results show that neuroligns are essential for regulating cognitive processing specifically involving cognitive flexibility and decision-making. These findings have relevance for understanding cognitive dysfunction in neurodevelopmental disorders where human mutations in NLGN genes have been extensively documented.

Touchscreen Learning in Genetic Mouse Models of Neurodevelopmental Disorders. Michael C Pride, Anna Adhikari, Nycole A Copping, Stela Petkova, and Jill L. Silverman. MIND Institute and Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, CA 95817. Until recently, cognitive tests for measuring learning and memory in animal models were underdeveloped in complexity, and with most commonly used tests employing on rudimentary stimuli and procedures. Most learning tasks are simplistic mazes and/or footshock-based paradigms. This uncritical use of behavioral paradigms may account for the low predictability of mouse models in psychiatric disorders. Newer assays of cognitive abilities for autism spectrum disorders (ASD) and intellectual disability (ID) include computerized assessments of simple learning, higher order cognitive flexibility and attention and impulsivity, which are more ideal because they are automated and avoid investigator interference that can have enormous influence on behavioral effects. Automation in preclinical assays is also more analogous to increasingly automated clinical testing for ASD and ID (e.g. NIH toolbox), and is able to measure multiple domains of cognitive abilities and build upon previously learned rules. Automated touchscreen technology has been employed for tasks of visual discrimination and reversal to identify affected circuits in models with genetic mutations associated with ASD and intellectual disability. We have optimized and tested these touchscreen assays in multiple models of genetic neurodevelopmental disorders. We tested mice with deletions and duplications in the chromosomal region 15q11.2, that lead to Angelman, Prader-Willi, and Dup15q Syndromes. All of these genetic disorders have substantial ID diagnosis and are co-morbid with ASD. Our studies revealed mutant mice were slower to reach criterion in the pairwise visual discrimination task and/or the reversal tasks. Open field activity and parameters of motor abilities were also measured to rule out and/or consider hypo- or hyperactivity as potential confounds in the touchscreen test. We conclude that these cognitive tests have better signal detection for subtle sophisticated behavior, such as cognitive flexibility. We conclude that our translationally relevant outcomes will expedite bench to bedside development of genetic, pharmaceutical and/or behavioral interventions.

9:30-11:30 **Symposium: What doesn't kill you makes you stronger! Exploring the biobehavioral mechanisms underlying resilience and adaptation to early-life adversity.** Chair: Susanne Brummelte, Wayne State University. Co-Chair: Amanda Kentner, MCPHS University.

Stress Resilience: A State of Mind, A State of Gut. Anand Gururajan[1,2], Ana Paula Ventura-Silva[2], Josh Lyte[2], Thorsten Becker[2], Marcel van de Wouw[2], Marcus Boehme[2], Barbara Merckx[1], Niamh Wiley[3], Gerard M Moloney[1,2], Catherine Stanton[3], Ted G Dinan[2,4], John F Cryan[1,2] 1Department of Anatomy & Neuroscience, University College Cork, Ireland, 2APC Microbiome Institute Science, University College Cork, Ireland, 3Food Biosciences Department, Teagasc Food Research Centre, 4Department of Psychiatry & Neurobehavioural, University College Cork, Ireland. Background: The perception of stress exposure varies between individuals and depends on whether they are stress-resilient or stress-susceptible. These divergent phenotypes are underscored by a variety of central and peripheral physiological processes. The aim of our study was to identify these processes using a chronic stress paradigm in mice. In particular, we analysed gene expression in the bed nucleus of the stria terminalis (BNST), a relatively understudied structure in this context, and examined the faecal microbiome as a predictor of response to the stress paradigm. Methods: Male C57Bl/6 mice were subjected to chronic psychosocial defeat stress after which they were tested for social avoidance behaviour to classify mice as being either resilient or susceptible. The day before the first and the day after the last defeat session, tail blood samples were collected for analysis of plasma corticosterone and faecal samples were collected for 16S-rRNA sequencing. Mice were culled the day after behavioural testing. The BNST was dissected out from brains and RNA was extracted for sequencing. Results: Peripheral corticosterone levels were higher in stress-susceptible than stress-resilient mice after the social defeat stress paradigm. At baseline, the relative abundance of the specific families of gut microbes was higher in stress-susceptible than stress-resilient mice. RNA-seq analysis of the BNST revealed differential expression of several genes between groups. Furthermore, in resilient mice we observed increased expression of Pac1r, a receptor for pituitary adenylate cyclase activating peptide which has previously been implicated in the response to chronic stressors. Conclusions: Consistent with recent literature, we have shown that stress resilience is defined by a complex molecular and physiological profile which spans central and peripheral compartments. Our faecal microbiome data indicates that gut bacteria may be a predictive biomarker of stress response and that the upregulation of Pac1r in the BNST is a neuromolecular mechanism which is critical for the development of stress resilience.

Please stop poking me! Influence of maternal care on the consequences of neonatal pain exposure in male and female rats. Dr. Susanne Brummelte[1] 1 Department of Psychology, Wayne State University, Detroit, MI, USA. Preterm infants are exposed to a many painful procedures while in the neonatal intensive care unit (NICU). Although these procedures are often necessary for the survival of the infant, recent research suggests that exposure to repeated painful procedures may result in impaired brain development. In addition, preterm infants also experience reduced maternal care while in the NICU and both stressor can have a profound negative impact on biobehavioral development. Our translational animal model investigates the biological and behavioral consequences of neonatal pain in combination with reduced maternal care and seeks to illuminate some of the underlying mechanisms of altered brain development. In our rodent model of NICU stressors, rat pups undergo a series of repetitive needle pokes and/or reduced maternal care through a novel tea-ball infuser encapsulation during the first four days of life. We analyzed the acute biological (neonatal) and the long-term (adult) biobehavioral outcomes and our results suggest that exposure to maternal isolation and neonatal pain produces an acute increase in serum corticosterone levels but a decrease in glutamate levels in the hippocampus and frontal cortex in neonatal animals. These neonatal changes may contribute to the observed altered hypothalamic-pituitary-adrenal axis function and changes in cognitive abilities in adulthood. Our findings suggest that neonatal pain and reduced maternal care can result in altered glucocorticoid and glutamatergic signaling that may contribute to long-term adaptation that actually enhance unique aspects of learning and will be discussed in terms of resilience to early-life adversity.

Harnessing the environment to promote resiliency to early life adversity. Amanda C. Kentner[1]. 1School of Arts & Sciences, MASACHUSSETTS COLLEGE OF PHARMACY AND HEALTH SCIENCES, Boston, MA 02115 amanda.kentner@mcphs.edu. Environmental enrichment is a protocol of enhanced stimulation; the key components of this condition appear to include

novel and diverse sensory experiences that can be introduced to both animals and humans. The utility of environmental enrichment in pediatric settings has shown success in autistic children and those at risk for cerebral palsy. However, the specific components of enrichment (e.g., sensorimotor stimulation, increased opportunities for social engagement, enhanced parental care) that may lead to clinical benefits are not understood. Perinatal exposure to infection is identified as a risk factor for neurodevelopmental disorders such as autism. Moreover, adverse experiences in early life can severely and profoundly reorganize the brain, leading to changes in function and related mental health outcomes. In our work, we use animal models of early-life inflammation, and other stressful experiences, to explore the potential for environmental enrichment to offer neuroprotection and remediation against associated cognitive and behavioral detriments. Moreover, we characterize the specific enrichment components and neuroendocrine mechanisms that underlie such benefits.

Epigenetic consequences of exposure to developmental adversity. T. L. Roth. Psychological and Brain Sciences, University of Delaware, Newark, DE 19716. In this talk I will highlight data from two lines of research in our laboratory exploring behavioral and molecular consequences of exposure to early adversity in the context of caregiving. In one line of research we utilized resource scarcity (i.e., insufficient nesting materials) to elicit adverse caregiving of rat offspring (postnatal days [PND] 1-7). When offspring were adult (~PND90), we observed sexually-dimorphic DNA methylation and behavioral alterations. In another line of research we repeatedly exposed rat mothers and their offspring (PND1-21) to a predator odor. When offspring were adolescents (PND30), we observed reduced fear behavior. Together, data are consistent with the notion that developmental adversity has effects on brain development that carry into later life to affect cognitive and emotional well-being. Further, data demonstrate that developmental adversity does not always lead to detrimental outcomes and can instead produce resiliency, including reduced stress responsiveness.

1:30-3:30 **Symposium: Neurobiology of cannabinoid type 2 receptors.** Chair: Hiroki Ishiguro, University of Yamanashi. Co-Chair: Emmanuel Onaivi, William Paterson University.

Cannabinoid type 2 receptors in dopamine neurons modify anxiety-like behaviors and alcohol and cocaine conditioned place preference. Canseco-Alba, Ana[1]; Onaivi, E[1] 1 William Paterson University. The endocannabinoid system consists of two receptor subtypes, CB1 and CB2 cannabinoid receptors, as well as the endogenous ligands (endocannabinoids) and the enzymes responsible for their biosynthesis and degradation. The role of the CB1 cannabinoid receptor on different behaviors is well documented. However, because initial studies were not able to detect CB2 receptor expression in the brain, the study of this receptor and its implications on behavior has been limited. CB2 receptor (CB2R) expression has been found in several brain areas and therefore it is likely that CB2R plays a potential role in a wide variety of behaviors and neuropsychiatric disorders, such as anxiety and substance abuse disorders. Recent findings support the role of CB2R in the regulation of anxiety and mood disorders. Studies shown that CB2R knockout mice have increased susceptibility to stressful stimuli. Also, transgenic mice that overexpress the CB2R (CB2xP) as an endo-phenotype are resistant to acute anxiogenic stimuli. On the other hand, there are reports suggesting that the CB2R plays a role in alcohol and cocaine related behavior. Intra-VTA administration of a CB2R agonist or the overexpression of CB2R in mouse brain inhibits or attenuates cocaine self-administration, respectively. A downregulation of the CB2R gene (Cnr2) expression in midbrain appears to be related to reinforcement for alcohol in mice. Using new genetic strategies like the generation of a conditional knockout mice, new possibilities are offered to study the role of the CB2R in specific behaviors. In this work, we evaluated the role of CB2R expressed in dopaminergic neurons in anxiolytic-like behaviors and in the rewarding properties of cocaine and alcohol using the conditioned place preference model (CPP) by using conditional knockout mice (cKO) that do not express the CB2R in midbrain dopamine neurons (DAT-Cnr2). We found that the DAT-Cnr2 cKO mice were less aversive to the open arms of the elevated plus-maze and the white chamber of the two-compartment black and white box than the wild type controls suggesting that CB2 receptors in dopamine neurons mitigate anxiogenic-like responses. We also found that DAT-Cnr2 mice do not show an alcohol-CPP induction, but they show an increase in CPP

induced by cocaine, evidencing that the role of the dopaminergic CB2R in the rewarding properties of cocaine and alcohol is distinctive.

Environmental stressors induce psychosis based on genetic variation of Cannabinoid CB2 Receptors. Hiroki Ishiguro[1], Kouichi Tabata[1], Chiaki Mochizuki[1], and Emmanuel S. Onaivi[2]. 1Department of Neuropsychiatry, University of Yamanashi Japan, 2Department of Biology, William Paterson University, USA. Major depression and alcoholism, as well as schizophrenia, are mental disorders somehow associated with stressful events in certain periods of lifetime and based on endocannabinoid related genetic background. Because a high incidence of functional polymorphisms in the Cannabinoid CB2 Receptor gene (CNR2) was found in all of depression, alcoholism and schizophrenia, the receptor must be one of the genetic factors. The expression of Cnr2 gene was regulated by methamphetamine treatment or by chronic mild stress. Putting those evidences together, we hypothesize possible functional relationships between some stressors and dysfunction of the cannabinoid Cb2 receptor which develop those psychiatric disorders. Naïve Cnr2 knockout mice did not show any difference in locomotion, sociability, prepulse inhibition and anxiety tests, which satisfied human psychiatric disorders as no apparent symptom was observed before onset. However, once Cnr2 knockout mice were treated with stress, they showed significant behavioral phenotype. We tested several stressors in mice as psychiatric disease models based on epidemiological evidences from previous studies. Methamphetamine was injected to those mice to examine their locomotion as acute response and as response at developed reverse tolerance. The Cnr2 knockout mice showed more locomotive activity after the acute treatment with them and also dramatic enhancement in locomotion after development of reverse tolerance for methamphetamine. After Poly I:C was injected i.p. to Cnr2 knockout mice, their locomotor activity reduced more and the anxiety on Zero maze increased in comparison to those of the wild type controls. The expression of either Fkbp5 or interleukins in Cnr2 knockout mice brain was differed after Poly I:C treatment, which indicate that Cnr2 is involved in HPA axis or in neuro-immune reaction when stressd. These findings were interpreted that mice with genetic dysfunction of CNR2 develop psychiatric behaviors if they experienced several stresses, including chemical and immune ones at adult age. Further studies are required to determine specific fragile age to the stressors based on each genetic background in the etiology of those psychiatric diseases. Our studies on Cannabinoid CB2 receptor may provide novel targets for the therapeutic potential of marijuana and cannabinoids in schizophrenia and depression.

Cannabinoid Receptor Genetics: From Mice to Human Subjects. Emmanuel S. Onaivi[1], Ana Canseco-Alba[1], Qing-Rong Liu[2], Hiroki Ishiguro[3] 1William Paterson University, Wayne NJ, 2Laboratory of Clinical Investigation, NIA-NIH, MD, USA 3Yamanashi University, Japan. Cannabinoids, and endocannabinoids (eCBs) activate two well-characterized cannabinoid receptors-(CBRs), CB1Rs and CB2Rs. Studies have shown that CNR and FAAH SNPs may contribute to drug addiction, depression, eating disorders, schizophrenia, and multiple sclerosis. Previous investigations have defined a number of features of the CNR1 gene's structure, regulation and variation. However, there are controversies over the CNS functional neuronal expression of the CNR2 gene. Nevertheless, our studies provided the first evidence for neuronal CNS effects of CB2Rs and its possible role in neuropsychiatric disorders and in rodent models of CNS function. The CNR1 and CNR2 genes are in human chromosome 6q15 and 1p36.11 respectively. Although CNR1 gene has more CPG islands than CNR2 gene, both have CPG islands less than 300 bases, but they may be regulated by DNA methylation. MicroRNA binding to the 3' untranslated region of the CNR1 gene with two polyadenylation site may also potentially regulate CB1R expression. CNR1 gene has 4 exons and there are 135 SNPs reported in more than 1% of the population with no common SNP that changes amino acids of CB1R currently known or reported. A copy number variant (CNV) which is 19.5kb found in 4 out of 2026 people covers exons 3 and 4 and codes amino acid that could alter the expression of CB1Rs. CNR2 has 4 exons with CB2A with 3 exons and CB2B with 2 exons; and there are about 100 SNPs found in more than 1% of the population, which include common cSNPs that change amino acids of the CB2R, including R63Q, Q66R and H316Y. Association studies were performed between polymorphisms in CNR2 gene and neuropsychiatric disorders in two independent case-control populations. We identified novel human and rodent CB2R isoforms with differential tissue expression patterns and regulation by CBR ligands. We report that there is association between polymorphisms of CNR2 gene and psychosis, eating disorders, depression and alcoholics in the human populations investigated. The ubiquitous CBRs -the most

abundant binding sites in the CNS- are known to be involved in a number of neuropsychiatric disturbances and have become major targets of investigation for their impact in neuropsychiatry. Therefore understanding the CBR genomic structure, it's polymorphic nature, subtype specificity, their variants and associated regulatory elements that confer vulnerabilities to a number of health disturbances may unravel the underlining mechanisms.

Microglial and dopaminergic-neuron-specific deletion of CB2 cannabinoid receptors in stress induced neuroinflammation and behavior. Branden Sanabria[1], Ana Canseco-Alba[1], Qing-Rong Liu[2], Hiroki Ishiguro[3] Emmanuel S. Onaivi[1]. 1William Paterson University, Wayne NJ, 2Laboratory of Clinical Investigation, NIA-NIH, MD, USA 3Yamanashi University, Japan. There is mounting evidence supporting the involvement of neuroinflammation in the development of mental illnesses. Psychological stress leads to the activation of the hypothalamus-pituitary adrenal (HPA) axis, impaired neurogenesis, reduced synaptic plasticity in the hippocampus, an excess of glutamate and cortisol, and monoamine depletion. Studies have also reported an increase in pro-inflammatory cytokines and microglial activation in mice exposed to acute and chronic stressors. Cannabinoids (CBs) found in Cannabis Sativa and endocannabinoids (eCBs) produced by our body elicit their physiological actions through two cannabinoid receptors (CBRs); Cannabinoid receptor type 1 (CB1R) and type 2 (CB2R). Although it is well accepted that CB1Rs are one of the most abundantly expressed receptors in the mammalian brain; the expression of CB2Rs was believed to be restricted to peripheral immune cells and responsible for the anti-inflammatory effects of marijuana. Therefore, the discovery of functional CB2 receptors in neurons and glia cells has raised questions regarding their role in regulating neuroinflammation and behavior. Studies have demonstrated the function of CB2Rs as a regulator of microglial activation, driving them towards a neuroprotective phenotype. Additionally, recent evidence has demonstrated that CB2Rs are responsible for modulating the hyperpolarization of hippocampal neurons, an area of the brain highly impacted by stress. Using the lox p technology we generated DAT-Cnr2 and Cx3cr1-Cnr2 conditional knockout mice, with CB2Rs conditionally knocked out of dopamine neurons and microglial respectively. We are characterizing the neuroinflammatory and behavioral responses after exposure to seven weeks of unpredictable chronic mild stress (UCMS). Immunofluorescent CD11b staining of the hippocampus revealed activated microglia after exposure to UCMS that was exacerbated in our conditional knockouts. Similarly there was increased immunoreactivity to iNOS, in the hippocampuse. Furthermore, CB2R conditional knockout mice displayed differences in sucrose and alcohol consumption after UCMS compared to their wild type C57BL/6J littermates. Overall our data using the cell selective deletion of CB2Rs from dopamine neurons and microglial identifies a neuro-immuno - cannabinoid activity cross-talk.

1:30-3:30 **Symposium: Nicotinic cholinergic signaling in neurological and psychiatric disorders: Insights from mouse models.** Chair: Vinay Parikh, Temple University, Philadelphia. Co-Chair: Jared W. Young, University of California at San Diego.

Impact of nicotine on aberrant reward processing in a mouse model of HIV. Samuel A. Barnes, Ph.D. [1], Jared W. Young[1], Ph.D., Igor Grant M.D[1], and TMARC[1] 1 Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0603, La Jolla, CA 92093, USA. Subjects with HIV have an increased smoking rate (50%) compared to the general population (16%). Smoking-related mortality is increased in HIV and so identifying the reason for this elevated consumption rate is necessary to identify potential strategies to aid smoking cessation in HIV. Transgenic mice expressing the HIV envelope glyoprotein, gp120, exhibit many features consistent with HIV-1, however, the impact of nicotine exposure on these features or behaviors related to risk-taking/reward-seeing remains unknown. Male mice (gp120 or wildtype littermate controls were implanted with iPRECIO programmable pumps filled with saline or nicotine (n=9-11/group). Performance in the effort-based decision-making (EBDM) task, probabilistic learning task (PLT), or progressive-ratio breakpoint (PRBP) task was assessed after (A) acute (single, 0.3 µl, 1.67 mg/kg/infusion), (B) chronic (5 x 1 hour infusions, 0.3 µl, 1.67 mg/kg/infusion over a 12-hour period for 16 days) or (C) withdrawal (4 hours post single infusion 0.3 µl, 1.67 mg/kg/infusion). Acute nicotine (A) treatment did not significantly affect performance in any task. After chronic exposure (B), a Treatment x Genotype interaction was evident for the EDBM [$F(1,34)=9.46, p<0.01$] and

PRBP [F(1,33)=5.47,p<0.05]. Compared to control animals, gp120 saline-treated mice exhibited increased preference for the high effort conditions (p<0.05); an effect attenuated by chronic nicotine treatment (p<0.05). No effect was observed in the PLT. During withdrawal (C), the elevated preference for effortful behaviors [EBDM: F(1,34)=6.00,p<0.05; PRBP: F(1,33)=5.37,p<0.05] was still evident in gp120 saline-treated mice (p<0.05), an effect reduced in gp120 mice during nicotine withdrawal (p<0.05). PLT accuracy was increased in gp120 mice undergoing nicotine withdrawal (p<0.05). Collectively, these findings suggest that elevated reward-based effort-cost computation and motivated behaviors in gp120 mice are elevated vs. wildtype littermates, an effect attenuated by nicotine treatment. The increased consumption of nicotine in HIV patients may reflect a self-medication approach to diminish abnormal elevations in motivated behavior. These data implicate a role for nicotinic acetylcholine receptors in the potential treatment of reward seeking motivated behavior in subjects with HIV-1

The role of α7 nicotinic acetylcholine receptors in neuroinflammation-mediated cognitive impairment. Kelly Dineley[1], IbDanelo Cortez[1], Egide Ishimwe[1], Caterina Hernandez[2] 1University of Texas Medical Branch at Galveston, 2Appalachaian College of Pharmacy. The α7 nicotinic acetylcholine receptor (nAChR), a ligand-gated ion channel that has garnered much interest since α7 nAChRs are found throughout peripheral tissues as well as being highly expressed in the CNS. In the periphery, α7 nAChRs have an essential role in the control of inflammation. Activation of the macrophage α7 nAChR selectively inhibits production of the pro-inflammatory cytokine tumor necrosis factor (TNF), interleukin-6 (IL-6) and IL-1β, among others, while leaving anti-inflammatory cytokines undisturbed. This cholinergic anti-inflammatory pathway is mediated by the vagus nerve. When afferent vagus nerve terminals are activated by cytokines or other pro-inflammatory stimuli, the efferent vagus nerve releases acetylcholine, leading to macrophage α7 activation and inhibition of pro-inflammatory cytokine production. In the CNS, α7 nAChRs are enriched in brain regions implicated in attention, learning and memory. However, α7 nAChR expression is not restricted to neurons; these receptors are highly enriched within the CNS innate immune system. We validated a neuroinflammation model in which intracerebroventricular LPS injection instigated a substantial CNS immune response as indicated by spikes in proinflammatory cytokines, including TNF-α, in the absence of a notable peripheral immune response. ICV LPS significantly impairs memory for the context associated with fear conditioning in α7 KO mice but not wildtype mice. Consistent with this neurobehavioral phenotype, α7 KO mice exhibit a more pronounced neuroinflammatory response (e.g., TNF-α). We have previously reported important roles for astrocytic α7 nAChRs in astrocyte-neuron communication via gliotransmission with subsequent effects on cognition. To extend these studies, we sought to test whether astrocytic α7 nAChRs serve an analogous role to that of macrophage α7 nAChRs in peripheral anti-inflammatory responses. Here we report on the contribution of astrocytic α7 nAChRs to the cognitive and pathological consequences of neuroinflammation using our floxed α7 nAChR mouse line interbred with GFAP-Cre mice.

Neurochemical circuit mechanisms underlying cognitive inflexibility in nicotine dependence. Vinay Parikh1, Robert D. Cole[1], Matty Zimmerman[1], Cassandra Wolsh[1], Anastasia Matchanova[1], Munir G. Kutlu[2] and Thomas J. Gould[2] 1Department of Psychology and Neuroscience Program, Temple University, Philadelphia, PA 19122 2Department of Biobehavioral Health, Pennsylvania State University, University Park, PA. The behavioral and cellular mechanisms underlying nicotine dependence are not fully understood. Cognitive flexibility is the ability to switch strategic responses adaptively in changing environments. It is possible that cognitive rigidity may foster maladaptive nicotine taking in addicts and increase relapse. Here we examined the effects of nicotine withdrawal on cognitive flexibility in mice using an operant strategy set-shifting task. Because frontostriatal circuits are critical for cognitive flexibility and brain-derived neurotrophic factor (BDNF) modulates glutamate plasticity in these circuits, we also explored the effects of nicotine withdrawal on these neurochemical substrates. Adult male C57BL/6J mice were exposed to either nicotine (6.3 mg/kg/d or 18 mg/kg/d) or saline using subcutaneous mini-osmotic pumps for 14 days. Spontaneous nicotine withdrawal was induced by removing the pumps and the animals were tested in an operant task that required them to switch from using a spatial response-driven strategy to a visual cue-based strategy to achieve rewards. Mice undergoing nicotine withdrawal required more trials to attain strategy switching criterion (F(2,22)=16.11, p<0.001). Error analysis show that animals withdrawn from both nicotine doses committed higher perseverative errors. However, animals treated with the

higher nicotine dose also displayed more strategy maintenance errors. Total BDNF and transcript IV BDNF mRNA expression increased in the prefrontal cortex (PFC) following nicotine withdrawal. Surprisingly, the level of the mature form of BDNF protein declined in the PFC ($p=0.02$) but was elevated in the dorsal striatum (DS; $p=0.02$) of these animals. DS BDNF protein inversely correlated with both perseverative and maintenance errors. BDNF-induced glutamate release and synapsin phosphorylation was suppressed in the DS of nicotine withdrawal mice ($p<0.01$ vs saline control). Nicotine withdrawal-mediated deficits in cognitive flexibility were attenuated by scavenging BDNF activity in the DS. Collectively, our findings indicate that cognitive inflexibility observed during nicotine withdrawal may presumably involve increased trafficking of BDNF from the PFC to DS and consequent alterations in glutamate plasticity. Efforts to develop therapeutic strategies aimed at normalizing aberrant BDNF signaling may minimize cognitive deficits in nicotine addicts and eventually lower the instances of relapse.

Chrna5 neurons in models of Alzheimer's disease: Consequences for neurophysiology in prefrontal cortex and beyond. Lambe, Evelyn[1]; Proulx, Eliane[1,2]; Sparks, Daniel[1]; Venkatesan, Sridevi[1]. 1University of Toronto, Canada 2Max Planck Institute of Neurobiology, Germany. Attention deficits are being increasingly recognized as one of the early and disabling symptoms of Alzheimer's Disease, and such deficits are recapitulated in rodent models. Control over attention is exerted by cholinergic modulation of the prefrontal cortex, with the major corticothalamic layer being robustly excited by acetylcholine. This layer expresses the conductance-modulating nicotinic receptor accessory subunit, Chrna5, and is involved in top-down regulation of attention as well as excitation of attention-relevant inhibitory local circuits. Our previous and ongoing work has shown that this cholinergic excitation of prefrontal cortex is muted in rodent models of Alzheimer's Disease. Here, we demonstrate the underlying mechanisms responsible using a combination of electrophysiology, optogenetics, and multiphoton calcium imaging. Intriguingly, the nicotinic receptor-elicited excitation is most impaired in layer 6, and this impairment is sensitive to manipulation of the SK family of calcium-activated potassium channels. In layer 6 neurons, increased afterhyperpolarizations seen with cholinergic stimulation, or in response to depolarization, appear to arise from increased sensitivity to calcium. Ongoing experiments probe the pathway of SK channel activation to permit improvements to existing treatments directed at increasing acetylcholine levels in prefrontal cortex and beyond.

1:30-3:30 **Symposium: Sensory processing and integration in neurodevelopmental disorders.** Chair: Susanne Schmid, University of Western Ontario. Co-Chair: Kaela Scott, University of Western Ontario.

Neurodevelopmental disruption of auditory processing in rats lacking the autism-candidate gene CNTNAP2. Brian L. Allman[1], Kaela E. Scott[1] and Susanne Schmid[1] 1Department of Anatomy and Cell Biology, Western University, London, ON. During early life, the auditory system normally undergoes tremendous development and plasticity; however, this typical maturation is perturbed in individuals with neurodevelopmental disorders, such as developmental language disorder (DLD) or autism spectrum disorder (ASD). The ability to accurately process sounds of varying intensities and temporal features is essential for the proper development of the auditory system. Indeed, the long-term consequences of developmental auditory deficits can be profound, often extending from disruptions in reflexive auditory behaviors to deficits in perceptual tasks and impaired language. Of the various genes that regulate auditory system development, CNTNAP2—which encodes a cell-adhesion protein (CASPR2) that is expressed throughout the auditory pathway—is strongly associated with ASDs and other language-related disorders. That said, it remained unresolved to what extent CNTNAP2 directly contributes to the developing brain's ability to process the basic features of sounds, such as its intensity and rapidly-changing temporal features. Thus, in the present study, we investigated the developmental trajectory of Cntnap2-related deficits in electrophysiological and behavioral measures of auditory brainstem and cortical function in juvenile, adolescent and adult rats. As juveniles, rats lacking Cntnap2 (Cntnap2-/-) showed a delay in sound-evoked neurotransmission throughout the early relay nuclei of their auditory system. Interestingly, by adulthood, this sluggish auditory brainstem response had fully recovered, yet other auditory processing deficits persisted. For example, extracellular electrophysiological recordings of neurons in the auditory cortex of adult Cntnap2-/- rats showed an inability

to respond reliably to rapidly-presented acoustic stimuli; findings indicative of a persistent auditory temporal processing impairment. Behaviorally, an assessment of each animal's reflexive responses to startle-eliciting sounds revealed an exaggerated acoustic reactivity as well as worsened sensory-motor gating with age in Cntnap2-/- rats compared to wildtype controls. Overall, the present study has shown for the first time that deletion of Cntnap2 causes a complex assortment of disruptions in auditory processing throughout development, and in doing so, we have validated a new rat model for studying auditory system dysfunction with high relevance to several neurodevelopmental disorders.

Cellular and Circuit Mechanisms of Neocortical Dysfunction in Autism Spectrum Disorder. Andreas Frick. Defects in sensory information processing play a major role in the clinical presentation of ASD. Given the role of sensory information processing for all behavioral functions, it is likely that alterations in sensory responsiveness are also causative of other autistic symptoms. Sensory information from various modalities is processed and integrated in the neocortex, making this brain area eminently suited for the evaluation of sensory-evoked signals. For example, an enhanced activation of the primary sensory areas of the neocortex following auditory, visual and tactile stimulation has been demonstrated in human subjects with ASD, compared to typically developing controls. In accordance with these findings in human subjects, we, and others, have demonstrated increased activity of the primary sensory neocortices (responsible for the integration of sensory information) in certain mouse models of ASD following sensory stimulation. Additionally, we demonstrated structural-functional connectivity alterations impinging on the sensory neocortex of the Fmr1–/y mouse. I will present our recent findings into the neuronal and circuit-level aberrations underlying these sensory defects.

Multisensory temporal function in autism: links to communication. Mark T. Wallace, Vanderbilt University. We live in a world in which we are continually bombarded with information from the different senses. Given that our perceptual view of the world is a unified one (rather than sense-by-sense), one of the major challenges for the brain is deciding which pieces of information belong together and which should be segregated. To accomplish this, the brain has a number of specialized areas and processing architectures. The first part of the talk will provide an overview of how individual neurons and ensembles of neurons within these areas respond to multisensory stimulus combinations. This work provides the foundation for the second part of the talk that will focus on studies examining how human performance and perception is altered under multisensory circumstances, with an emphasis on development. These developmental studies are predicated on the view that there is a shift from an early reliance upon simple statistical features of multisensory stimuli (e.g., spatial and temporal relations) to a later dependence upon higher-order factors such as task and context. The final part of the talk will focus on autism spectrum disorders, and will be framed from the perspective that this neurodevelopmental disability whose clinical presentation revolves around changes in social communication, is also characterized by significant changes in sensory and multisensory function. Indeed, we believe that these (multi)sensory changes play an instrumental role in shaping the changes seen in social communicative function.

CNTNAP2 modulates the developmental trajectory of vocal communication in mice. Marta Fernandez, Teresa Sierra, Mikel Larranaga, Irene Mollinedo-Gajate, Olga Penagarikano. Department of Pharmacology, University of the Basque Country (UPV/EHU), Leioa 48940, Spain. The study of vocal communication in animal models provides key insight into the evolution of language and the neurogenetic basis for speech and communication disorders. Several animal models, such as song birds and bats, have proven to be powerful for this purpose, as they present with similarities to learned human speech and are well-studied in laboratory settings. In the recent years, the mouse is becoming a valuable tool for research on speech and language development, as they are now recognized to display some components of human language, and mutations in genes that affect language development also affect vocal communication in mice. One such genes is CNTNAP2, which has been extensively implicated in language development and language elated disorders. CNTNAP2 genetic variants have been associated with autism (a disorder with language and communication deficits), dyslexia, specific language impairment as well as with language development in the general population. Further, FOXP2, a transcription factor whose dysfunction has been shown to cause developmental speech and language disorder, regulates CNTNAP2 expression, indicating they are part of a circuitry essential for human language. We have previously shown that a mouse knockout for the Cntnap2 gene display abnormal vocal communication as shown by reduced number

and irregular type of ultrasonic vocalizations emitted in pups upon maternal separation at postnatal day 7. Ultrasonic vocalizations are classified into several syllable types, which are believed to infer important information for vocal communication. Although the developmental trajectory of syllable types has been studied in other models of vocal communication, little is known about the normal developmental course of vocal communication in mice. In the present work, we found that absence of CNTNAP2 in mice leads to an abnormal developmental trajectory in the pattern of emission of ultrasonic vocalizations compared to wild-type. These abnormalities could potentially be associated to neuroarchiteture defects found in cortico-striatal circuits in this model. Additional work will provide insight into the molecular contribution of Cntnap2 in vocal communication. This work was supported by MINECO/FEDER grant SAF2015-64163-R, BBVA Foundation Grant for Researchers and Cultural Creators, NARSAD Brain and Behavior Foundation grant 23663 to OP. OP is a Ramon y Cajal Fellow (RYC-2013-12558). MF is a MINECO predoctoral fellow (BES-2016-078420).

4:00-6:00 **Symposium: Disruptions of parental experiences: Neurobiological and behavioral effects in parental responsiveness and offspring development**. Chair: Molly Kent, University of Richmond.

Paternally-mediated transgenerational plasticity in stickleback fish. Alison M. Bell[1]. 1University of Illinois, Urbana-Champaign. The environment experienced by parents – including the social environment – can influence the behavioral development of their offspring. From an adaptive point of view, it would be advantageous if parents could detect cues about the type of environment their offspring are likely to experience and then somehow prepare their offspring for living in that environment (adaptive transgenerational plasticity). Here, I will introduce a species well-suited for examining the effects of fathers experience on offspring: threespined stickleback fish. In this species, fathers are the sole providers of parental care that is necessary for offspring survival. Individual stickleback fathers vary in the type and quality of care they provide for their offspring, and variation in paternal care has consequences for the growth, behavior and survival of their offspring. Moreover, offspring of fathers that experienced danger in the environment (predation risk), grew up to have predator-adapted phenotypes. I will show how we are studying the molecular, epigenomic, behavioral and physiological mechanisms by which stickleback fathers influence the development of their offspring in an adaptive manner, and argue for its evolutionary significance.

Multigenerational impact of female opioid exposure on offspring metabolic risk factors. Fair M. Vassoler[1], Anika M. Toorie[1], Elizabeth M. Byrnes[1]. 1Tufts University Cummings School of Veterinary Medicine. Endogenous opioids modulate the reproductive axis, influencing physiological and behavioral processes across the lifespan. Women are increasingly exposed to exogenous opioids in the form of prescription opioids, including morphine, codeine, and oxycodone. This increased exposure may result in significant effects on future reproductive function. Using the rat as a preclinical model, we have documented a number of significant effects of both prenatal and preconception opioid exposure on maternal responding. Moreover, additional effects can be observed in their female offspring and grandoffspring. Thus, the effects of opioid exposure in females may impact future generations by altering reproductive processes.

Sex-dependent neuroendocrine, neuroinflammatory, and behavioral responses to paternal deprivation in the biparental California mouse (Peromyscus californicus). Glasper, Erica, R.[1, 2], Khantsis, Sabina[1], Walker, Shakeera, L.[2], Madison, Farrah, N.[1, 2]. 1Department of Psychology, University of Maryland, College Park, Maryland, 20742, US, 2Program in Neuroscience and Cognitive Sciences, University of Maryland, College Park, Maryland, 20742, US. In human and non-human animals alike, early-life experiences with caregivers can significantly alter offspring development. Much of our knowledge concerning these parent-offspring relationships stem from studies investigating uniparental rodent species, in which maternal rodents are the sole source of parental care. Increasing evidence suggests that relations between fathers and offspring may be of equal importance, especially in species that require paternal care for survival and/or typical development. In a number of biparental model systems, presence of the father can prevent social, behavioral, and neurological impairments, which appear early and have enduring consequences into adulthood. Using a unique model of paternal deprivation in the biparental California mouse (Peromyscus californicus), my lab recently

demonstrated that paternal deprivation leads to increased neonatal mortality, decreased locomotion, and increased passive-stress coping behavior during a task of behavioral despair. Interestingly, we also observed a sex-dependent effect of paternal deprivation on short-term survival of newborn cells in the dentate gyrus of the hippocampus. Specifically, paternal deprivation reduced cell survival in female, but not male, young adult California mice. Given that numerous factors are implicated in the inhibition of neuronal proliferation and survival in the hippocampus, we performed experiments that elucidate potential mechanisms contributing to sex differences in neuroplasticity as a result of paternal deprivation in the biparental California mouse. In a series of experiments, we demonstrate a sex-dependent corticosterone response to acute and chronic stress following paternal deprivation. Additionally, paternal deprivation differentially alters proinflammatory cytokine concentration and the density of microglia in the hippocampus of males and females. Furthermore, we provide evidence that suggests paternal deprivation results in sex-dependent alterations to recognition memory and generalized anxiety.

An investigation of restricted environmental resources, threat presence and maternal responsiveness on offspring brain and behavioral development. Molly Kent, University of Richmond, Richmond, VA. When rats provide parental care for offspring mothers must rely on available environmental resources which will determine the quality of care available to offspring. Limiting nesting resources results in atypical maternal care which has consequences on the development of offspring. Female rats were provided with standard or low nesting materials (low), with and without presence of threat commencing at parturition investigating consequences on offspring development and cognition. During early development low mothers exhibited interrupted responsiveness in the home cage; specifically, standard groups had a significantly higher overall maternal index score. Additionally, maternal retrieval was assessed with a challenge task in which standard groups exhibited faster average pup retrieval and threat groups exhibited longer retrieval times. Endocrine and neurological data indicate standard mothers have increased resilience seen with a higher DHEA/CORT ratio and increased NPY-immunoreactivity. Standard offspring had longer tails, while low and threat pups were heavier at parturition. The differences in tail length and body weight continued throughout adulthood. Hormone analysis showed significantly higher baseline levels of CORT in the low, threat exposed group compared to all other groups. Behavioral testing showed cognitive deficits in both social and stress responsivity of female offspring. The threat and low groups showed decreases in overall interaction with the novel object indicating an increased stress response. When female cagemates were confined in the novel object, the no threat group showed more behaviors focused around the cagemate. When a novel male was confined in the object differences were observed in the no threat compared to the threat groups. Duration of nose to nose contact with the novel male was highest in the no threat standard group. Histological data show a trend toward higher levels of oxytocin in the supraoptic area in the no threat group. Combined together the research indicate that limited resources and threat presence during lactation can result in long-term changes tooffspring. Decreases in available resources and presence of threat can alter maternal responsivity resulting in long term changes in offspring. Therefore, the prevalence of poverty in human families requires relevant translational research to further illuminate the effects of limited resources and stress on maternal and offspring well-being.

4:00-5:45 **Oral Session 2:** Chair: Davide Amato, Medical University of South Carolina

Synergistic effects of maternal immune activation and adolescent cannabinoid exposure on schizophrenia-related behaviour and prediction error responses in rats. Ariel Dunn[1,2], Lauren Harms[1,2], Abbey Mateer[1,2], Ross Fulham[1,2], Gavin Cooper[1], Juanita Todd[1,2], Deborah M. Hodgson[1,2], Patricia T. Michie[1,2]. 1University of Newcastle, Callaghan, Australia, 2Priority Research Centre for Brain and Mental Health Research, UON, Australia. The development of animal models that reliably recapitulate features of schizophrenia is essential for understanding the neurobiology of the disorder, as well as the preclinical development of new treatments. The neurodevelopmental multiple hit hypothesis suggests that schizophrenia is not caused by one factor alone, but rather a combination of risk factors across a lifetime. This series of studies investigated the impact of maternal immune activation (MIA) during prenatal life combined with a second 'hit' of adolescent cannabinoid exposure (ACE) on schizophrenia-related behaviour and prediction error responses commonly altered in schizophrenia. Pregnant Wistar rats were exposed to either Poly(I:C) (MIA) or saline during late gestation (day

19). Offspring were then exposed to HU-210, a synthetic cannabinoid (ACE), or vehicle for 14 days during early adolescence. A cohort of adult animals underwent surgeries to implant skull electrodes to assess prediction error responses using EEG, similar to the human mismatch negativity. Another cohort of rats were tested on a variety of behavioural tasks. All rats exhibited prediction error responses, a significant increase in the skull-recorded potential after a surprising stimulus that defied a predicted regularity. Male animals exposed to ACE alone (CON-ACE), as well as two-hit males (MIA-ACE) had significantly reduced predictive error responses, compared to control animals (CON-VEH). Prepulse inhibition and social recognition were reduced in two-hit females (MIA-ACE) versus controls (CON-VEH). Two-hit females (MIA-ACE) also had increased marble burying compared to females exposed to ACE alone. No significant effects of MIA or ACE were observed for behaviour in male animals. Our two-hit model of MIA x ACE was sufficient to produce schizophrenia-like reductions in predictive error responses in males. These findings indicate that predictive coding mechanisms are impaired in male two-hit rats, with possible ramifications for cognitive functions such as attention. In contrast, the novel findings of schizophrenia-like alterations in prepulse inhibition, social recognition and marble burying were observed in female animals only. In combination, our findings suggest that males may be more sensitive to cortical processing and predictive coding deficits associated with the two risk factors, while females are more sensitive to the behavioral changes.

The therapeutic potential of cannabidiol (CBD) in a transgenic mouse model of Alzheimer's disease. Georgia Watt[1], Carolin Schumacher[1], Arne Ittner[2], Magda Przybyla[2], Lars Ittner[2], Henry Li[3,4], Brett Garner[3,4] and Tim Karl[1,2,5] 1Western Sydney University, School of Medicine, Campbelltown, Australia 2University of New South Wales, School of Medical Sciences, Kensington, Australia 3University of Wollongong, Wollongong, Australia 4Illawarra Health and Medical Research Institute, Wollongong, Australia 5Neuroscience Research Australia, Randwick, Australia. Background: Pathological brain changes in Alzheimer's disease (AD) include the accumulation of amyloid-β (Aβ) and tau hyperphosphorylation causing neurodegeneration, neuroinflammation and oxidative stress. Current AD treatments do not stop or reverse the disease progression, highlighting the need for more effective therapeutic alternatives. The non-psychoactive phytocannabinoid cannabidiol (CBD) has demonstrated anti-oxidant, anti-inflammatory and neuroprotective properties. Furthermore, our previous work found chronic CBD treatment (20 mg/kg) to reverse social recognition memory deficits and to have subtle effects on neuroinflammatory markers (e.g. TNF-α and IL-1β) in an established mouse model for AD (i.e. APPxPS1 transgenic mice). The current project aimed to determine the chronic effects of 50 mg/kg CBD in the APPxPS1 model and the tauopathy mouse model of AD, the Tau58/2 mice. Methods: Male APPxPS1 at 12 months of age and male Tau58/2 mice at 3 months of age were treated with CBD (50 mg/kg CBD, daily intraperitoneal injections) starting 3 weeks prior to behavioural testing. A variety of cognitive domains including social recognition memory, spatial memory, and fear-associated memory as well as motor function were evaluated following the initial treatment period. After testing, brain tissue was collected, and AD relevant brain pathology was investigated (i.e. Aβ and tau pathology and neuroinflammatory markers [e.g. TNF-α, IL-1β and IL-6]). Results: In male APPxPS1 mice CBD treatment reversed a social recognition memory deficit and trended to reduce insoluble Aβ40 levels in the hippocampus. CBD treatment did not restore motor deficits in the Tau58/2 males. The study in Tau58/2 mice also revealed this mouse model does not exhibit impairments in social recognition or fear associated memory. Conclusions: Our study indicated that 50mg/kg CBD was able to reverse cognitive deficits and to modulate Aβ pathology of male APPxPS1 mice. CBD had no effect on behavioural impairments in the Tau58/2 males. This research was funded by Dementia Australia Research Foundation (DARF) and CBD was supplied by GW Pharmaceuticals.

Microglia program anxiety and stress regulating brain regions early in life. Lars H Nelson1, Spencer Warden2, Kathryn M Lenz1,2,3,4. 1Neuroscience Graduate Program, 2Department of Neuroscience, 3Department of Psychology, 4Institute for Behavioral Medicine Research, The Ohio State University. Microglia, the brain's resident immune cells, regulate brain development, including cell genesis, cell death, myelination, axon guidance, and synaptic patterning. We have previously shown that reversibly depleting microglia from the brain during the early postnatal period decreases anxiety, behavioral despair, and the acute stress response in adulthood. The mechanisms through which microglia impact the early life programming of mood-related behavior at baseline or in response to early life perturbations remains unknown. To probe

the mechanisms through which microglia contribute to early life programming of behavior, we centrally infused liposomal clodronate (2µL icv; Encapsula Nanoscience) in male and female rats on postnatal days (P) 1 and 4, which temporarily depletes 90% of forebrain microglia for ~1 week. To determine the brain region(s) responsible for the dampened stress response that we previously observed, we assessed the number of neurons expressing cFos, a marker of neural activation, in limbic brain regions after acute restraint stress in adults. We found decreased cFos expression in the medial prefrontal cortex (mPFC) in clodronate-treated rats relative to controls. The mPFC is a brain area that regulates anxiety and the stress response, suggesting there could be decreased recruitment of stress regulating brain areas following early life microglia depletion. We are currently assessing cFos expression in the amygdala, another region that regulates anxiety and the stress response. Interestingly, we have also found no changes in dendritic spine density or neuronal morphology in the mPFC and are currently examining the amygdala. Microglia are known to regulate synaptic patterning and developmental myelination, thus we also assessed expression of genes related to inhibitory synapses (vGat), dendritic spine synapses (spinophilin), and myelin proteins (Mbp, Plp1), in the mPFC and amygdala at P6, P12 and P22 following microglia depletion. Relative to controls, Mbp and Plp1 were decreased at P12 in the amygdala and mPFC, but only decreased in the amygdala at P22, vGat was increased in the amygdala at P12, but not in the mPFC, and there was no difference in spinophilin expression. Together, these results suggest that microglia may organize later-life behavior by regulating myelination and/or inhibitory interneuron function during development. Together, these results begin to elucidate the role microglia play in the development of mood-related behavior.

Exposure to fluoxetine during adolescence in female C57BL6 mice results in an anxiogenic-like behavioral phenotype in adulthood. Sergio D. Iñiguez[1], Francisco J. Flores-Ramirez[1] 1Department of Psychology, University of Texas, El Paso, TX. Accumulating preclinical evidence indicates that early-life exposure to psychotropic medications results in altered behavioral responses to stress in adulthood. However, to date, these preclinical experimental approaches have been conducted primarily using male subjects. This is surprising given that females, when compared to males, are more likely to be diagnosed with mood-related disorders, and thus, to be prescribed with psychotropic medications such as antidepressants. To examine if altered sensitivity to anxiety-inducing situations are exhibited in adulthood, as a result of juvenile exposure to antidepressants, we exposed adolescent female c57bl/6 mice to the selective serotonin reuptake inhibitor (SSRI) fluoxetine (FLX). We selected FLX given that it is the only SSRI approved by the US Food and Drug Administration for the treatment of pediatric depression. Specifically, female mice were forced to consume FLX in their drinking water (250 mg/L) from postnatal day [PD]-35 to PD49, and were later assessed in adulthood (PD70+) on responsivity to the elevated plus-maze and the light-dark box test – traditional behavioral paradigms used to assess anxiety-like responses in rodents. Our results show that adult female mice pretreated with FLX during adolescence spent less time in the open arms of the elevated plus-maze, when compared to saline-pretreated controls. Similarly, when tested on the light-dark box, FLX-pretreated mice displayed significantly longer latencies (sec) to enter the light-side compartment of the testing chamber, and spent significantly less time (sec) within this compartment, when compared to controls. No differences in locomotor activity were evident between the groups as a function of SSRI pre-exposure. Collectively, our data suggest that adolescent exposure to FLX mediates behavioral adaptations that endure into adulthood, which are indicative of a generalized anxiogenic-like phenotype, in female mice.

DYRK1A as a prototype of gene involved in neurodevelopmental disorders. Lessons learnt from modeling in the mouse and in the rat. Herault, Yann[1,2] ; Dubos, Aline[1] ; Duchon, Arnaud[1] ; Nguyen, Thu Lan[1] ; Maréchal, Damien[1] ; Chevalier, Claire[1] ; Pani, Guillaume[1] ; Muniz Moreno, Maria del Mar[1] ; Brault, Véronique[1]. 1Institut de Génétique Biologie Moléculaire et Cellulaire, IGBMC, CNRS, INSERM, Université de Strasbourg, UMR7104, UMR964, 1 rue Laurent Fries, 67404 Illkirch, France. 2Institut Clinique de la Souris, PHENOMIN-ICS, CNRS, INSERM, Université de Strasbourg, 1 rue Laurent Fries, 67404 Illkirch, France. Neurodevelopmental disorders (NDD) induce early onset impairments of the brain development and function that impacts adaptive functioning in the conceptual, the social or the practical domain with or without other features. Several genetic causes, including deletion or duplication of genomic regions, and more than 800 genes, have been associated with NDD. We focused our interest on 2 NDD that are due to copy number variation of the Dual Specificity Tyrosine Phosphorylation Regulated Kinase 1A (DYRK1A): the Mental Retardation disease 7 due to

mutation in the gene causing intellectual disabilities, Autism spectrum disorders and epilepsy and Down syndrome or trisomy 21 one of the most common form of ID in which DYRK1A is main driver gene. Here we will report the characterization of models mimicking the MRD7 and DS conditions using genetic and pharmacological approaches with standardized behavioural and cognitive paradigms. In addition we went further deciphering the origins of the phenotypes using conditional approaches, combined with cellular and molecular studies. The data generated are challenging our current knowledge on the role of DYRK1A, suggesting different time- and tissue-dependent mechanisms are perturbed in both disease conditions. Such studies offer perspectives for a better understanding of MRD7 and DS and how the cognition and behaviour is affected in human.

Early SSRI exposure disrupts long-term behavioral responses to social and sensory stimuli. Susan E. Maloney[1], Shyam Akula[1], Katherine B. McCullough[1], Krystal Chandler[1], Joseph D. Dougherty[1]. 1Washington University in St. Louis School of Medicine. Serotonin (5HT) helps to direct behavioral responses to environmental stimuli, likely through its influence on neuroplasticity. High levels of 5HT may render individuals more sensitive to environmental stimuli and low 5HT less sensitive. Levels of 5HT, its receptors and transporter peak during development, a time during which 5HT plays widespread tropic roles. The high levels during development are likely important for the developing brain to respond to the external environment and promote proper maturation of behavioral circuits. Social behavior and sensory processing are disrupted in nearly all psychiatric disorders, including neurodevelopmental disorders (NDDs). Serotonergic dysregulation is also implicated many NDDs. Thus, we are interested in how changes to 5HT activity during brain development might influence responses to social and sensory stimuli later in life, as related to NDDs. We developed a model of maternal SSRI exposure to disrupt the developing 5HT system and examined the behaviors of the offspring. Specifically, we exposed mouse dams to fluoxetine during gestation and lactation, and characterized offspring behavior as pups and adults. In SSRI-exposed offspring, we found robust dampening of isolation-induced pup ultrasonic vocalizations, and adult perseverative behaviors, increased social dominance, and tactile hypersensitivity. These results suggest altering 5HT activity during development disrupted pup responses to the early social environment, and altered circuitry involved in the responses to the environmental, social and sensory stimuli later in life. To identify if changes to the 5HT system by maternal SSRI exposure are responsible for these behaviors, we re-exposed an independent cohort of mice to SSRI as adults in an attempt to rescue the behavioral deficits. SSRI treatment during adulthood partially rescued the tactile hypersensitivity but further increased the dominance phenotype. These results suggest disrupting 5HT levels during development influenced the role of the 5HT system in the behavioral circuits responsible for responses to sensory and social stimuli in these tasks, but in opposite directions. Specifically, SSRI treatment ameliorated the hypersensitivity to sensory stimuli but further exacerbated the response to social stimuli. On the whole, our findings suggest 5HT-mediated sensitivity to external stimuli may play a role in the neurobiology of social behavior and sensory processing disruptions common in NDDs.

Characterising and exploiting δ subunit-containing $GABA_A$ receptors as novel targets for treating social disorders. Bowen, Michael T[1]; Jones, Kathryn[1]; Chebib, Mary[2] 1The University of Sydney, School of Psychology and Brain and Mind Centre, Australia; 2The University of Sydney, Faculty of Pharmacy and Brain and Mind Centre, Australia. No pharmacological treatments are available for the dysfunctional social behaviour at the core of many disorders, such as autism spectrum disorder (ASD) and social anxiety disorder. A dominant theory in social neuroscience is that normal social behaviour relies on a delicate excitatory/inhibitory (E/I) balance in specific brain regions. Disturbances in social behaviour have been linked to an underlying dysfunction in GABAergic neurotransmission and a subsequent shift towards excitation. Most of these studies have focused on synaptic GABAAR mediated phasic inhibition, which leads to powerful but short-lasting reductions in excitation in specific neural circuits. Unfortunately, drugs targeting synaptic GABAARs have disappointed in trials. A novel alternative is to target tonic inhibition, controlled largely by extrasynaptic δ subunit-containing GABAARs (δ-GABAARs), which regulates E/I balance through long-lasting, network-level inhibition of neuronal excitation. Our recent data from rodent studies provides the first solid evidence that δ-GABAARs are critically involved in social behaviour and we have effectively targeted these receptors pharmacologically to alleviate social deficits in a mouse model of ASD. More specifically, we showed that mice lacking δ-GABAARs have pronounced deficits in active social behaviour in the

dyadic social interaction test and reduced preference for social novelty. Importantly, the behaviour of these mice is normal in tests of locomotor activity, generalised-anxiety-like behaviour and olfactory perception. We then explored whether we could target δ-GABAARs to restore normal social behaviour in the BALB/c mouse model of ASD. Relative to C57BL/6 mice, BALB/c mice had reduced active social investigation, increased passive social contact, and a lack of social preference. Treatment with the δ-GABAAR-preferring agonist 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol (THIP) resulted in social interaction behaviour and social preference in the BALB/c mice that was equivalent to that observed in the C57BL/6 mice. Studies are underway exploring the neural circuits in which tonic inhibition might act to mediate social behaviour and to discover and develop safer treatment alternatives to THIP. Overall, our findings to-date demonstrate for the first time that extrasynaptic GABAARs play a crucial role in regulating social behaviour and provide a novel therapeutic target for treating social disorders.

Sex differences in brain-resident immune cells and the early life programming of social behaviors Kathryn M. Lenz, PhD, Douglas Vanderhoof, Aarohi Joshi, BS. Department of Psychology, Department of Neuroscience, Institute for Behavioral Medicine, The Ohio State University, Columbus, Ohio, 43209, USA. Early life inflammation increases the risk for male-biased neurodevelopmental disorders such as autism and ADHD. We seek to determine how sex differences in brain-resident innate immune cells and their activity contribute to this sex bias in risk. Perinatal inflammatory challenge alters the development of social behavior and males are more susceptible to inflammation-induced disruptions in juvenile social play behavior (Taylor et al., 2011). We have found that innate immune cells called mast cells are more abundant in the male brain during development than in the female brain. We used immune challenge with lipopolysaccharide (LPS) on postnatal day (PN) 1 and concurrent pharmacological inhibition of mast cells with cromolyn to test whether mast cells contribute to inflammation-induced alterations in social play. We found that LPS induced significant increases in social play behavior in males only that were prevented by co-treatment with cromolyn. To determine if LPS leads to sex-specific mast cell signaling, we performed a Bioplex ELISA to measure cytokines known to be released by mast cells and LC/MS for histamine, serotonin and their byproducts on brain samples from pups obtained 1 hour following LPS or LPS + cromolyn treatment on PN1. We found that LPS induced increases in proinflammatory cytokines in males only, and in females, LPS led to increased histamine turnover and levels of interleukin 13, a mast cell mediator, in response to LPS. Co-treatment with cromolyn prevented these changes. We hypothesize that female mast cell mediators may be protective against inflammation-induced alterations in social behavior. Together, these studies show that mast cells may be an unappreciated contributor to the brain's inflammatory response, and that sex differences in mast cells contribute to sex differences in the brain's response to early life inflammatory events.

4:00-5:30 **Symposium: Factors influencing replicability of behavioral neuroscience studies.** Chair: Polymnia Georgiou, University of Maryland School of Medicine. Co-Chair: Todd D. Gould, University of Maryland School of Medicine.

Replication of Genome-Wide Association Studies (GWAS) of Behavioral and Physiological Traits in an Advanced Intercross Mouse Line. Abraham A Palmer[1], Xinxin Zhou[1], Natalia Gonzales[2] [1]University of California San Diego, Department of Psychiatry, La Jolla, CA 92093, [2]University of Chicago, Department of Human Genetics, Chicago, IL 60637. Abstract: Genome wide association analyses (GWAS) in model organisms have numerous advantages compared to human GWAS, including the ability perform experimental manipulations; however, the extent to which results from mouse GWAS can be replicated is not well defined. We have identified a large numbers of genome-wide significant loci for behavioral, physiological, and gene expression traits in mice from the advanced intercross line (AIL), which is an intercross between two inbred strains that has bene maintained as an outbred population. We will discuss these results with an emphasis on replication across three cohorts that have been studied over a period of more than ten years: F34 (n= 688), F39-43 (n=600), and F50-56 (n=1,063). We have replicated many loci that were identified in the earlier studies of this intercross, including an association between locomotor activity and a locus containing a single gene, *Csmd1*. We also showed that Csmd1 mutant mice recapitulated the locomotor phenotype. Our results demonstrate the utility of

this population, identify numerous novel associations, and provide examples of replication in an independent cohort, which is customary in human genetics, and replication by experimental manipulation, which is a unique advantage of model organisms.

Assessing replicability of mouse behavioral genetic studies through aggregated experimental results Elissa J. Chesler, Vivek M. Philip, Molly A. Bogue. The Jackson Laboratory, Bar Harbor, Maine, USA. A major challenge in the replicability of behavioral genetic studies is the sensitivity of behavioral outcomes to the diverse environmental states in which testing occurs. This variation includes experimental apparatus, testing conditions, housing, laboratory environment and husbandry procedures. Replication in the strictest sense of the word seeks to obtain the same experimental result given the same conditions through the implementation of reproducible research protocols. However, such replication of findings is highly limited to context, and therefore the ultimate goal of replication, which is obtaining a result that is generalizable to other contexts, is poorly assessed. Aggregation of data from behavioral genetic experiments designed to assess the same measurement in diverse experimental conditions provides different approaches to assessing replicability. In one approach, the genotype by laboratory environment interaction is assessed from studies of similar measures across multiple strains of mice in multiple environments. This provides an estimate of the minimum effect size of a finding that one could expect to replicate across laboratories for a comparable measure, a parameter which can be included in Benjamini's Random Laboratory Model for assessment of replicability in a single laboratory study. In a second approach, reliability and trait correlation analysis is an estimate of the replication of genetic findings across studies and populations. In a related approach, results of aggregate behavioral genetic studies can be combined through meta-analysis to test the joint and replicable association of a variant to a trait or set of traits. This genetic meta-analysis can be performed at the level of individual measures or a collection of traits which share annotation to a common ontology term. These approaches are all implemented in the Mouse Phenome Database, which provides a platform for the complex trait research community to share and analyze rigorously curated behavioral genetic data across multiple populations and assays.

Human experimenter sex modulates mouse behavioral responses to stress and to the antidepressant ketamine. Polymnia Georgiou[1] (Ph.D), Panos Zanos[1] (Ph.D), Carleigh Jenne[1] (BS), Jaclyn Highland[1] (BS), Danielle Gerhard[4] (MS), Ronald Duman[5] (Ph.D), Todd D. Gould[1,2,3] (MD) Departments of Psychiatry1, Pharmacology2, and Anatomy & Neurobiology3, School of Medicine, University of Maryland, Baltimore, MD, USA. Departments of Psychology4 and Psychiatry5, Yale university, CT, USA. Lack of replicability of experimental results may be due to unexpected experimental variables that are not appropriately controlled for in experimental designs. Rodents can differentiate the sex of human experimenters, which may affect responses. We investigated experimenter sex effects on stress-induced behaviors in mice, and the reversal of such behaviors by the antidepressant drug ketamine. We showed that a female compared to a male experimenter conducting procedures induced resilience to anhedonia following chronic social defeat stress (CSDS), decreased development of helpless behavior following inescapable shocks and decreased immobility time in the forced-swim test (FST). Consistent with the published literature, when administered by a male experimenter, ketamine reversed CSDS-induced anhedonia, reduced escape failures following inescapable shock training and decreased immobility time in the FST, while antidepressant responses were absent when ketamine was administered by a female experimenter. Ketamine administration by female experimenters decreased alpha EEG power. Similar experimenter sex-dependent effects were identified with ketamine's active metabolite (2R,6R)-hydroxynorketamine, but not with other classical or fast-acting antidepressants and another NMDAR antagonist. The nearby presence of a female experimenter was sufficient to block antidepressant actions of male-administered ketamine. We also showed that elimination of experimenter scents, did not result in antidepressant actions regardless of the sex of the experimenter. Pretreatment with corticosterone prior to ketamine administration within a biosafety cabinet by a female experimenter resulted in antidepressant effects, whereas pretreatment with a CRF1 antagonist by a male experimenter blocked ketamine's effects suggesting that the sex of human experimenter affects mouse stress levels resulting in differential effects with the antidepressant drug ketamine. Overall, these findings demonstrate the importance of experimenter sex to the outcome of behavioral assessments and

antidepressant response to ketamine. Our data argue that experimenter sex may affect replicability, and that experiment sex should be considered as an important experimental variable.

6:30-8:30 Poster Session 2:

1. Effect of microglial suppression by pre-treatment of the periadolescent rat with minocycline on nicotine-induced sensitization to cocaine reward in the adult. Brooke E. Svenson, Partha S. Nagchowdhuri, Helen L. Williams, Brian A. McMillen. Dept. of Pharmacology & Toxicology, Brody School of Medicine at East Carolina University, Greenville, NC 27834 USA. The use and abuse of alcohol and other drugs often originates with the onset of puberty by experimentation with tobacco and other substances that are readily available to that young age group. Periadolescent exposure to nicotine can lead to the brain's sensitization to other drugs of abuse later in life (Adriani et al., J Neurosci 23:4712, 2003; McMillen et al., Eur J Pharm 509:161, 2005; James-Walke et al. Neurotox Teratol 29:31, 2007): a result that suggests a long-term change in neural connections. Microglia activation plays a role in some long-term adaptive changes in the brain and may have a role in this sensitization. Minocycline is a tetracycline antibiotic that is used experimentally to suppress activation to the M1 polarization of microglial cells within the brain. The hypothesis that when rats are treated with minocycline before each exposure to nicotine that they will not develop a sensitization to cocaine due to their lack of activated microglia cells was tested in the following experiment. This study used four groups of male Sprague-Dawley rats: vehicle, 0.4 mg/kg nicotine, 30 mg/kg minocycline (30 min prior) + 0.4 mg/kg nicotine, and 30 mg/kg minocycline. All drug doses were corrected for the free base. Once daily i.p. injections were made for 10 days, PND 35-44, which bracket the peripubertal period. The sensitization to nicotine was tested with a cocaine-induced conditioned place preference (CPP) paradigm. Adult rats (starting on PND 80) were tested in a three-chamber CPP apparatus. Days 1-3 each rat was allowed free exploration for 15 min; Day 3 movements of each rat were recorded using the Behavior program written by Prof. L.W. Means; Days 4, 6, 8, 10 each rat received 3.0 mg/kg i.p. cocaine and was immediately confined to their least preferred side; Days 5, 7, 9, 11 each rat received the vehicle and was confined to their preferred side; Day 12 no drugs were injected and each rat's movement was recorded again for 15 min. The conditioning with cocaine increased the time spent in the least preferred chamber by 58% in the vehicle-exposed group and 109% in the nicotine-exposed group. The change in seconds (mean ± sem) for time spent in the least preferred chamber was as follows: Vehicle = 100 ± 27, Nic = 218 ± 40*, Min + Nic = 225 ± 47*, Min = 98 ± 49 (*different from Vehicle, $p < 0.05$). There was no difference between the Nic and the Min + Nic groups. The minocycline only group was the same as the Vehicle group. These data suggest that activation of microglia cells may not be necessary for the sensitization to nicotine administered during periadolescence.

2. Drebrin regulates opiate-induced behavioral and structural plasticity in the NAc. Jennifer A. Martin[1], Craig T. Werner[1], Ping Zhong[2], Zi-Jun Wang[1], Justin N. Siemian[1], Devin Hagarty[3], Rachael L. Neve[4], Jun-Xu Li[1], Ramesh Chandra[5], Mary-Kay Lobo[5], Amy M. Gancarz[3], Zhen Yan[2], David M. Dietz[1] 1Department of Pharmacology and Toxicology; Research Institute on Addictions, University At Buffalo 2Department of Physiology and Biophysics, University at Buffalo 3Department of Psychology, California State University, Bakersfield 4Deparment of Brain and Cognitive Sciences, Massachusetts Institute of Technology 5Department of Anatomy and Neurobiology, University of Maryland School of Medicine. Opiate addiction, a chronic relapsing disease, places a large societal and financial burden on our country. In particular, the fundamental issue for the therapeutic treatment of opiate addiction is the persistent drug craving, seeking, and high rates of relapse following drug abstinence. These behaviors are characterized by persistent behavioral and cellular plasticity in key regions of the mesolimbic dopamine system such as the nucleus accumbens (NAc), including structure and density of dendritic spines on Medium Spiny Neurons (MSNs). To date the cellular and molecular mechanism governing opiate-induced structural plasticity remains undetermined. Following heroin self-administration we find decreased expression of the essential actin-binding protein drebrin in the NAc, an effect that is transcriptionally regulated through HDAC2 binding on the drebrin promoter. Using viral mediated gene transfer, overexpression of drebrin

attenuated, while CRISPR-Cas9 deletion exacerbated, heroin-primed, but not sucrose primed, relapse-like behaviors. In addition, drebrin overexpression produced a downward, while CRISPR-Cas9 produced an upward, vertical shift in a within-session dose-response curve; demonstrating drebrin regulates the reinforcing properties of heroin. Restoration of drebrin levels following heroin self-administration reversed the heroin-induced decreases in spine density and reduction in AMPA and NMDA receptor conductance. Taken together, these data demonstrate an essential role for drebrin in mediating the molecular mechanisms underlying opiate-induced behavioral and structural plasticity. More importantly, understanding these cellular responses will help lead to the therapeutic intervention for the prevention of relapse.

3. Neuroinflammatory Modulation of Nicotine Dependence, Erin L. Anderson[1], Adewale Adeluyi[1], and Dr. Jill R. Turner[1], 1University of South Carolina. Neuroinflammation and associated gliosis has been demonstrated to be a primary mediator of many neurological disorders, including in CNS trauma, ischemia, stroke, and neurodegenerative diseases. However, while their role has been extensively examined in neurology, this is much less true in psychiatry, especially in substance use disorders. It is thought that discrete microenvironments in the select brain regions may polarize the immune effector cells, namely microglia, to a reactive state. One region reliably shown to underpin many behavioral characteristics of substance use disorders as well as the withdrawal symptomology is the nucleus accumbens (ventral striatum). Our preliminary data indicates that significant neuroinflammation can be detected in the ventral, but not the dorsal striatum, following withdrawal from chronic nicotine in mice. Furthermore, previous studies have suggested that microglial activation can contribute to neuronal damage through release of reactive oxygen and nitrogen species and inflammatory cytokines. In line with these findings, we detect significantly increased levels of both reactive oxygen species as well as pro-inflammatory cytokines in the ventral, but not dorsal, striatum. Furthermore, treatment with antioxidant compounds result in prevention of anxiety-like nicotine withdrawal phenotypes. Our current experiments investigate whether pharmacological compounds possessing both structurally and mechanistically distinct mechanisms for inhibiting microglial activation, such as ibudilast and minocycline, will reduce the molecular and behavioral hallmarks of neuroinflammation during nicotine withdrawal. Further, because these processes are known to be able to regulate nicotine-induced upregulation and assembly of nicotinic acetylcholine receptors, a phenomenon that can be correlated to anxiety-like nicotine withdrawal behaviors, future studies will examine the effects of these inhibitors on modulating nicotinic receptor expression.

4. Is there a cognitive cost to inhibiting cocaine relapse with mGlu5 receptor antagonism? Gobin, Christina[1]; Schwendt, Marek[1] 1University of Florida. Cocaine addiction produces corticostriatal neuroadaptations that may contribute to relapse. Changes within this circuitry might also underlie cognitive dysfunction that could further increase relapse susceptibility. Indeed, abstinent cocaine addicts exhibit hypoactivity of the prefrontal cortex (PFC) which coincides with cognitive deficits. It is not clear if analogous “hypofrontality” and deficits can be observed in rat models of persistent cocaine-seeking. In the current study, “the incubation of cocaine craving” model was used in order to investigate post-cocaine cognitive function and relapse. Rats underwent extended-access cocaine self-administration or received saline infusions. During abstinence, rats were tested in an operant delayed-match-to-sample (DMS) task that evaluates working memory and a delayed non-match-to-sample task to assess reversal learning. Chronic cocaine produced working memory impairment and a slight deficit in reversal learning. Within the PFC, we used (1) quantitative cytochrome oxidase histochemistry to evaluate metabolic activity and (2) western blotting to analyze protein expression of the metabotropic glutamate receptor 5 (mGlu5), a master regulator of synaptic plasticity. We show negative correlations between PFC metabolic activity and mGlu5 protein expression with cognitive task performance. These data suggest that task difficulty involves upregulation of proteins important for synaptic plasticity. Considering this, it is important to note that glutamatergic transmission from corticostriatal projections permits drug relapse. Blocking this glutamate transmission through antagonism of mGlu5 has indeed been shown to attenuate relapse. However, cognitive side-effects of prolonged blockade of mGlu5 are poorly understood. Here, we sought to determine the effect of

chronic mGlu5 inhibition on working memory and relapse. After cocaine self-administration, rats established baseline performance in the DMS task. Next, rats received systemic injections of MTEP or vehicle for five days followed by a washout period of five days. Finally, rats underwent a context + cue relapse test with MTEP or vehicle onboard. We showed that while MTEP attenuated relapse, chronic treatment impaired working memory performance. Our results suggest the need to evaluate cognitive function when investigating possible mGlu5-based pharmacotherapies of cocaine relapse.

5. Cocaine seeking ensembles in the medial prefrontal cortex following early and late abstinence. Megan Slaker[1], Natalie N. Nawarawong[1], Christopher M. Olsen[1]. 1Neuroscience Research Center and Department of Pharmacology & Toxicology, Medical College of Wisconsin, Milwaukee, WI. Neuronal ensembles are small sets of neurons whose activity is required for manifestation of a behavior. Previous studies have identified ensembles in fear and reward memory that are sufficient to drive behavior. In the current study, we sought to examine the generalizability of drug-seeking ensembles within the medial prefrontal cortex. Drug-seeking behaviors are persistent and will increase over periods of abstinence. Thus, we examined the drug-seeking ensembles during early and late abstinence from cocaine self-administration. We used the dual transgenic TetTag reporter mouse model that uses the c-Fos promoter to drive expression of the EGFP-histone-2B fusion protein tag. Doxycycline (dox) suppresses the expression of the tag, allowing temporal resolution on production of the tag. First, mice were trained to self-administer cocaine (0.5mg/kg/infusion) under a fixed ratio-1 (FR1) schedule of reinforcement for at least 7 days with dox present in their diet. Following training, mice underwent a period of forced abstinence, with cocaine-seeking sessions on day 7 (early) and day 21 (late). Seeking on day 7 was tagged with EGFP and seeking on day 21 was visualized by immunohistochemistry for c-Fos. We observed elevated levels of responding on days 7 and 21 compared to the final training day. Additionally, we found that the greater proportion of ensemble cells activated during both 7 and 21 day seeking sessions was correlated to a higher degree of cocaine-seeking behavior. However, most human drug use does not occur in one environment, but instead spans multiple settings. Contextual cues can reinstate drug seeking even when operant responding has been extinguished in a different environment. Therefore, we examined the association between drug-seeking ensembles and contexts. TetTag mice were trained to self-administer cocaine in two distinct contexts. Seeking on day 7 was tested in one context and tagged with EGFP, while seeking on day 21 was tested in the other context and assessed for c-Fos. In both contexts, mice were able to learn self-administration and show elevated levels of seeking. Future analysis will examine the similarities and differences between populations of ensemble cells identified in each context, as well as those labeled by both contexts. These studies provide insight into the ability of contextual cues to trigger seeking behaviors at a neuronal level.

6. The effects of chemogenetic inhibition of prelimbic cortical inputs to the paraventricular nucleus of the thalamus on cue- and cocaine-induced drug-seeking behavior in sign-trackers vs. goal-trackers. Kuhn, Brittany[1]; Campus, Paolo[1], Klumpner, Marin[1]; Flagel, Shelly[1] 1University of Michigan. Relapse remains the biggest problem in the treatment of addiction, with rates as high as 90%. Cues associated with the drug-taking experience can turn into powerful motivators and elicit drug-seeking behaviors via Pavlovian learning. However, there is individual variation in the extent to which a cue can attain such motivational value and only when it is attributed with incentive salience does it gain inordinate control over behavior. To study the underlying neural mechanisms, we use an animal model that captures individual variation in the propensity to attribute incentive salience to reward-paired cues. In this model, sign-trackers (STs) are rats that attribute incentive salience to a reward-predicting cue, and will approach and manipulate the cue upon its presentation; whereas goal-trackers (GTs) assign only predictive value to the cue and go to the location of reward delivery upon cue presentation. Relative to GTs, STs are also more impulsive, have higher cocaine break-point and are more susceptible to cue-induced reinstatement of drug-seeking behavior. The paraventricular nucleus of the thalamus (PVT) has been recognized for mediating cue-motivated behaviors, including individual differences in the propensity for cue-induced relapse. However, the specific PVT circuitry mediating this variation in drug-seeking behavior remains unknown. The prelimbic

cortex (PrL) sends dense projections to the PVT, and has been implicated in addiction-related behaviors. Using the ST/GT model, recent data from our lab shows that this pathway mediates the incentive value of reward cues. The current study used a dual-vector inhibitory (Gi) DREADD (Designer Receptors Exclusively Activated by Designer Drugs) to examine if inhibition of the PrL-PVT pathway differentially mediates cocaine-seeking behavior in STs vs. GTs. Rats were characterized as STs or GTs based on their behavior during a Pavlovian conditioned approach task and then underwent 2 weeks of cocaine self-administration followed by 4 weeks of abstinence and then extinction training. Prior to the tests for reinstatement, rats received either clozapine-N-oxide to activate the DREADD, or vehicle. Preliminary results suggest that inhibition of the PrL-PVT pathway increases drug-seeking behavior in STs during a cocaine-induced reinstatement test. These findings will further our understanding of the neurobiological mechanisms mediating relapse, and can lead to novel targets for the treatment of addiction.

7. Resolving the neural circuitry of Social Familiarity induced Anxiolysis (SoFiA) using Gi-DREADDs. S. Majumdar[1,2,3], A. Abreu[2,3], E. A. Lungwitz[1,2,3], N. Bharadwaj[1,3], K. D. Andrews[2,3], A. D. Dietrich[1,3], W. A Truitt[1,2,3]. [1]Depts of Anatomy & Cell Biology, [2]Stark Neurosciences Research Institute, [3]IU School of Medicine. A crucial aspect of healthy social behavior involves learning to adapt emotional responses to social cues, for example learning to suppress anxiety through social familiarity, or social familiarity-induced anxiolysis (SoFiA). SoFiA is well documented and forms basis for interpersonal therapy, however, the neural mechanisms of SoFiA are unclear. SoFiA is modeled in rats by employing social interaction habituation (SI-hab) protocol. Using SI-hab protocol it has been determined that SoFiA represents social safety learning, which requires both anxiogenic stimulus (Anx) and social familiarity (SF) during training sessions (5-6 daily social interaction sessions), and SoFiA expression is dependent on infralimbic cortex (IL). Based on these findings we hypothesize that Anx and SF are processed by unique neural systems, and repeated convergence of these signals interact within IL to induce plasticity resulting in social safety learning and anxiolysis. Here we investigated the role of IL in SoFiA acquisition and expression, using hM4D(Gi) recombinant adeno-associated virus AAV5-CAMKIIa-hM4D(Gi)-mCherry and CNO (exogenous ligand for Gi-DREADDS) to inhibit IL neurons/axons. Rats received bilateral viral injections (200nL) targeting IL and after 6 weeks, we found that i.p. injections (30 min prior to testing) of CNO (0.5mg/kg), but not vehicle, completely blocked SoFiA acquisition (n=10). CNO injection in rats that had acquired SoFiA (vehicle gr) completely blocked SoFiA expression. Experiments to better understand which IL afferents and efferents are pivotal for SoFiA are ongoing. In a pilot study we targeted IL efferents to basolateral amygdala (BLA) by intracranial bilateral injection of CNO (3µM,100nL) into BLA of Gi-DREADDs rats (i.e. rats with viral injections in their IL). These Gi-DREADDs rats underwent SI-hab protocol and acquired SoFiA (sham i.c. injections were given 10 min prior to each SI session, for sessions 1-6). Next day, rats then received bilateral CNO injections into the BLA, 10 min prior to the 7th session. These CNO injections blocked SoFiA expression, suggesting that IL efferents to BLA are putatively involved in SoFiA expression..

8. A role for the histone lysine demethylase KDM6B in Alcohol Use Disorder (AUD) and neuroinflammation. Vilca SJ[1,2], Johnstone AL[1,2], Andrade, NS,[2], Barbier E[3], Khomtchouk BB[1,2], Rienas CA[1,2], Lowe K[1,2], VanBooven DJ[4], Tapocik JD[5], Meinhardt MW[6], Sartor GC[1,2], Zeier Z[1,2], Sommer WH[6], Heilig M[3], Wahlestedt C[1,2] 1Center for Therapeutic Innovation and the 2Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL; 3Department of Clinical and Experimental Medicine, Division of Cell Biology, Faculty of Health Sciences, Linköping University, Linköping, Sweden; 4John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami FL; 5Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD; 6Department of Psychopharmacology, Central Institute of Mental Health, Mannheim, Germany. Alcohol use disorder (AUD) is a chronic relapsing brain disease characterized by uncontrolled drinking that leads to tolerance and symptoms of psychological and physical withdrawal. Despite years of research, the molecular mechanisms underlying this debilitating disease are not well known. Recently, epigenetic modifications to DNA and histones

have been shown to be dysregulated following chronic alcohol use in the human and rodent brain. However, the mechanisms regulating these epigenetic modifications remain unclear. Using Nanostring nCounter, quantitative qPCR, and western blot analyses, we found that KDM6B, a JMJ-domain containing histone lysine demethylase, was altered in the prefrontal cortex (PFC) and nucleus accumbens (NAc) of alcohol-dependent male, Wistar rats. KDM6B mRNA was found to be enriched in microglia relative to neurons and astrocytes, and ChIP-seq analysis revealed an increase of H3K27me3, the primary target of KDM6B, at multiple genes involved in inflammation in the PFC and NAc of post-dependent rats. In in vitro studies, KDM6B was increased following LPS treatment in BV2 cells (mouse microglia cell line), while KDM6B knockdown and overexpression blunted and enhanced cytokine production (IL-6, TNF-a), respectively, following LPS stimulation. GSK-J4, a selective KDM6B inhibitor, also decreased IL-6 expression in BV2 cells treated with LPS in a dose dependent manner. In ongoing in vivo studies, a role for KDM6B in alcohol-seeking behavior and alcohol-induced neuroinflammation is being explored. Together, these results indicate that KDM6B mediates a proinflammatory response in vitro and may be, in part, responsible for neuroinflammation induced by chronic alcohol use.

9. Maternal care effects on anxiety and alcohol consumption. Ashley Bui[1], Nicole M. Cameron[1]. 1Binghamton University. Natural variations in maternal care during early life has profound effects on offspring later in life. In rats, low maternal care levels correlate with greater anxiety in the elevated-plus maze and early-life maternal separation correlates with increased ethanol consumption and preference. Here we investigated the effects of natural variations in licking/grooming (LG) during postnatal days 1-6 on anxiety-like behaviors and alcohol consumption in Long Evans adult rats. In Experiment 1, we examined differences in anxiety-like behavior in high versus low LG rats. Animals were tested in the light/dark box (LDB) for five minutes (females in proestrus), and two days later (females in metestrus) in the elevated T maze (ETM) for five minutes for three inhibitory avoidance (IA) trials followed by three escape latency (EL) trials. High LG males spent more time in the light portion of the LDB compared to low LG males. This effect was not found in females. While in the ETM, low LG females spent more time in the closed arm during IA trials compared to high LG females. No effects were found in the EL trials. In Experiment 2, we examined alcohol consumption in high and low LG rats utilizing a two-bottle sucrose tapered test involving 12 days (3 days/week for 4 weeks) of 18 hours of exposure to 10% ethanol and vehicle (1% sucrose Week 1, 0.5% Week 2, 0% Week 3-4). We found sex and phenotype effects such that females preferred ethanol compared to males and low LG animals preferred ethanol compared to high LG animals. We also found that ethanol preference increased over time, but this effect was driven by low LG females' increase in preference. The same effects were found when analyzing ethanol consumption (g/kg), whereas total fluid (vehicle and ethanol) consumption (g/kg) was only affected by sex, as females consumed more than males. A week after this two-bottle test, a one-bottle 2-hour 10% ethanol consumption test also revealed that low LG females consumed more 10% ethanol than high females and males. In summary, these behaviors indicate that low maternal care may have anxiolytic and substance use susceptibility effects later in life; furthermore, low maternal care seems to affect females more in terms of this alcohol consumption. With the substantial effects maternal care has on anxiety behavior and alcohol consumption, it would be vital to investigate whether the neural mechanisms driving these behaviors also overlap.

10. Zebrafish Responds To Alcohol In The Water Before It Reaches Its Brain. Benjamin Tsang [1], Steven Tran [2], Hayden Chow [3], Robert Gerlai [1,4] 1 Department of Psychology, University of Toronto Mississauga 2 Current address: Division of Biology and Biological Engineering, California Institute of Technology 3 Faculty of Science, University of Western Ontario 4 Department of Cell and Systems Biology, University of Toronto. The practicality and simplicity of alcohol administration in the zebrafish has made it an increasingly popular animal model for the study of alcohol abuse, addition, and tolerance. Despite the vast literature detailing the behavioral responses in zebrafish induced by alcohol treatment, none have explored whether or not the zebrafish can detect alcohol in their environment immediately after immersion. We argue that the ability for an animal to detect a drug in their surroundings before the mechanistic actions in the brain take effect is crucial for proper behavioral analysis and

interpretation. In our study, we placed zebrafish singly into a 1.5 L tank filled with 1% alcohol solution, and recorded their behavior in high-definition. We subsequently analyzed the time course of behavioral changes over the 60-minute recording session that started with zebrafish being immersed in the alcohol solution, and discovered a time dependent effect of alcohol. In addition to using automated software to track zebrafish movements, we also employed manual observation-based quantification of behavior. Previously, alcohol was found, or was assumed not to have an immediate effect, suggesting no peripheral action and no immediate detection of this substance by zebrafish. Our findings disprove these past results and refute this assumption. At 1% v/v EtOH concentration, we found that within the first 3 minutes of exposure, zebrafish decreased their distance to bottom and increase their absolute turn angle. We suggest behavioral changes occurring before alcohol could reach the brain in an appreciable level (i.e. within 10-15 min after the start of immersion into alcohol solution) can only be due to peripheral effects, e.g. the fish sensing this drug in the water. Our results thus suggest that zebrafish are able to detect alcohol in their environment immediately after exposure, a finding that has implications for alcohol choice test paradigms.

11. The role of lateral intercalated cell masses of the amygdala in social buffering of conditioned fear responses in male rats. Kiyokawa, Yasushi[1]; Minami, Shota[1]; Takeuchi, Yukari[1]. 1Laboratory of Veterinary Ethology, The University of Tokyo. In social buffering, stress responses are less distinct when an animal is exposed to a stressor with conspecific animals. In male rats, the presence of a non-conditioned accompanying rat (associate) mitigated a wide variety of stress responses when a fear-conditioned subject was exposed to an auditory conditioned stimulus (CS). In this social buffering, the olfactory signal from an associate activated the posterior complex of the anterior olfactory nucleus (AOP), which in turn suppressed the lateral amygdala (LA). However, at this time, it remains unclear whether the AOP directly suppresses the LA by activating its GABAergic neurons or indirectly suppresses the LA by activating other nuclei that are capable to suppress the LA. The intercalated cell masses of the amygdala (ITCs) are clusters of GABAergic neurons and surround the basolateral complex of the amygdala. Among the ITCs, in vitro analyses suggested that the lateral ITC (lITC) was capable to suppress the LA. Based on these findings, it would be reasonable to hypothesize that the lITC is involved in social buffering if the AOP indirectly suppresses the LA. To clarify these points, we prepared a fear-conditioned subject that was exposed to the CS either alone or with an associate. We confirmed that an associate mitigated both behavioral responses and Fos expression in the paraventricular nucleus of the hypothalamus of the subject. During this social buffering, Fos expression in the AOP was increased, which was not preferentially expressed in the GABAergic neurons. In addition, Fos expression in the lITC was increased by an associate. Fos expression in the medial ITCs was also changed during social buffering. Based on these findings, we propose that the AOP indirectly suppresses the LA by activating lITC in social buffering.

12. Light vs. dark or black vs. white? Illumination vs. background shade preference in the light dark task using zebrafish. Amanda Facciol[1], Robert Gerlai[1,2] 1University of Toronto, Department of Cell & Systems Biology 2University of Toronto Mississauga, Department of Psychology. The light dark task has been highly useful in screening anxiolytic compounds and investigating neural mechanisms underlying anxiety-related behaviour in rodents. Recently, the light dark paradigm has been adapted for use in zebrafish. Due to their evolutionarily conserved systems and highly prolific nature, zebrafish are expected to allow for high throughput analysis of anxiety related mechanisms. However, the use of zebrafish in the light dark paradigm has resulted in inconsistent findings. Some researchers report zebrafish to have a preference for light, whereas others, a preference for dark. We suggest these results may be due to confusing multiple environmental factors that may have differential effects on anxiety responses in zebrafish. Two such factors are the level of illumination and the shade of the background. Even within the same paper, some use the term "light" interchangeably with "white" and "dark" with "black. Here, we systematically investigate the preference for background shade vs. illumination using newly designed preference tanks. To investigate illumination preference (i.e. light vs. dark), zebrafish were placed into either an all white or all black tank with only one side illuminated (a divider down the centre allows for stark

illumination contrast between the light and dark compartments). For shade preference (i.e. black vs. white), zebrafish were placed into a half white, half black tank with even illumination throughout. Our lab has previously shown that zebrafish exhibit a preference for light over dark when manipulating illumination level. In contrast, we found here that zebrafish exhibit a preference for black over white within the first 3 minutes of the test session when manipulating background shade. This black preference was associated with an increase in anxiety related behaviours, such as bottom dwelling. We are now investigating the interaction between shade and illumination preference by manipulating the level of illumination within the shade preference task. We are also investigating whether ethanol, a drug with anxiolytic properties, alters choice behaviour in the background shade and illumination preference test. Our results reconcile previously inconsistent findings by showing that illumination level and background shade are two distinct factors that differentially alter zebrafish choice behaviour.

13. Effects of intranasal orexin-A on MK-801-induced attentional deficits. Eden B. Maness[1], Jim R. Fadel[2], Joshua A. Burk[1] 1College of William & Mary 2University of South Carolina School of Medicine. Schizophrenia (SZ) is a debilitating condition wherein those afflicted experience positive symptoms, such as hallucinations and delusions, as well as negative symptoms, which include alterations of processing that affect cognition and social interactions. The NMDA receptor hypofunction model of SZ asserts that widespread failure of cortical inhibition – resulting from reduced NMDA receptor input to GABA interneurons – yields excessive cortical and subcortical excitation and produces the cognitive deficits in this condition. Orexin-A (OxA), a neuropeptide principally involved in wakefulness, appetitive behaviors, and motivation has also demonstrated cognitive-enhancing qualities in both typical and atypical conditions. In the present experiment, the effects of OxA on attentional performance were examined in an NMDA receptor antagonist model of SZ. Male Fischer 344 Brown Norway F1 Hybrid rats (N = 12) received both intraperitoneal injections of MK-801 and intranasal administration of OxA prior to performing a visual sustained attention task. OxA either failed to rescue or impaired attentional accuracy following exposure to MK-801. In particular, as the degree of NMDA receptor antagonism increased, the highest OxA concentration worsened the correct rejection of the signal, whereas both intranasal saline and the low OxA dose had no impact across MK-801 dose. These findings suggest that, in a state of NMDA receptor antagonism-induced overstimulation of frontal and midbrain regions, augmenting the activity of the orexinergic system further exacerbates attentional dysfunction.

14. Effects of intranasal orexin-A on MK-801-induced attentional deficits. Eden B. Maness1, Jim R. Fadel2, Joshua A. Burk1 1College of William & Mary 2University of South Carolina School of Medicine. Schizophrenia (SZ) is a debilitating condition wherein those afflicted experience positive symptoms, such as hallucinations and delusions, as well as negative symptoms, which include alterations of processing that affect cognition and social interactions. The NMDA receptor hypofunction model of SZ asserts that widespread failure of cortical inhibition – resulting from reduced NMDA receptor input to GABA interneurons – yields excessive cortical and subcortical excitation and produces the cognitive deficits in this condition. Orexin-A (OxA), a neuropeptide principally involved in wakefulness, appetitive behaviors, and motivation has also demonstrated cognitive-enhancing qualities in both typical and atypical conditions. In the present experiment, the effects of OxA on attentional performance were examined in an NMDA receptor antagonist model of SZ. Male Fischer 344 Brown Norway F1 Hybrid rats (N = 12) received both intraperitoneal injections of MK-801 and intranasal administration of OxA prior to performing a visual sustained attention task. OxA either failed to rescue or impaired attentional accuracy following exposure to MK-801. In particular, as the degree of NMDA receptor antagonism increased, the highest OxA concentration worsened the correct rejection of the signal, whereas both intranasal saline and the low OxA dose had no impact across MK-801 dose. These findings suggest that, in a state of NMDA receptor antagonism-induced overstimulation of frontal and midbrain regions, augmenting the activity of the orexinergic system further exacerbates attentional dysfunction.

15. A novel task for studying reconsolidation-related memory updating in rats: a role for muscarinic receptors. Cassidy E. Wideman[1], Chelsea MacGregor[1], Courtney Kupka[1], Krista A. Mitchnick, Boyer D. Winters[1]. 1Department of Psychology and Collaborative Neuroscience Program, University of Guelph, Guelph, ON, Canada. Memory reconsolidation likely plays a role in the dynamic and flexible storage of long-term memories. This process begins with reactivation, which can destabilize consolidated memories into a labile or modifiable state and necessitates a period of protein synthesis-dependent reconsolidation to re-stabilize the memory. Long-term memories most reliably destabilize under reactivation conditions that present the opportunity for memory updating (i.e. novelty). We have recently reported that novelty-induced destabilization of object memories is regulated by cholinergic activity in the perirhinal cortex, a brain region critically involved in object memory. Accordingly, M1 muscarinic receptor antagonism within the perirhinal cortex prevents object memory destabilization induced by novelty. Furthermore, our findings suggest that novelty-induced stimulation of M1 receptors can cause downstream activation of the ubiquitin proteasome system (UPS), suggesting a physiological correlate for memory destabilization in the form of synaptic protein degradation. We are currently investigating the intracellular pathway on linking M1 receptors and the UPS in this paradigm and its relevance to the widespread theory that reconsolidation subserves memory updating. To this end, we have developed a novel behavioural task to demonstrate measurable behavioural modification following reconsolidation. In a variation of the standard object recognition task, we have assessed whether novel contextual information can become incorporated into an existing object memory if presented immediately following object memory destabilization (i.e., during the reconsolidation window). Our data suggests that the novel context becomes associated with the object and, as a result, during testing rats treat the object as familiar when presented in the novel context despite not having actually experienced the object within that context; this effect is both reactivation- and time-dependent, as exposure to the context 6 h after object memory destabilization does not produce the same behavioural change. We are currently investigating the effects of muscarinic receptor antagonism on this behavioural modification, as we predict that the mechanism we have implicated in object memory destabilization is necessary for the actual updating of the same memory. This research should help to demonstrate directly the involvement of reconsolidation and related neural mechanisms in constructive memory updating.

16. Optogenetic inactivation of basolateral amygdala in young rats recapitulates aged rats' ability to delay gratification in an intertemporal choice task. Caesar M. Hernandez[1,4], Caitlin A. Orsini[2,4], Joseph A. McQuail[1,4], Matt M. Bruner[1], Chase Labiste[1], Alexa-Rae Wheeler[1], Tyler W. Ten Eyck[1], Sarthak Singhal[3], Sara N. Burke[14], C. Jason Frazier[3,4], Barry Setlow[2,4], Jennifer L. Bizon[1,4] Departments of 1Neuroscience, 2Psychiatry, 3Pharmacodynamics and 4McKnight Brain Institute, University of Florida, Gainesville Florida. Intertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. Such decisions require integration of existing reward representations (prior experience) with valuation of the organism's current wants and needs (incentive motivation). Prior studies in both humans and rodents show that relative to young adults, aged subjects are better able to delay gratification, and generally prefer large, delayed over small, immediate rewards. While the neural circuit and molecular changes that mediate these age differences in intertemporal choice are unknown, lesion studies consistently implicate the basolateral amygdala (BLA) in motivation and affective decision making. The current experiments used optogenetic approaches to determine the effects on choice behavior of temporally discrete BLA inactivation during an intertemporal choice task. Young adult (6 mo) and aged (24 mo) Fischer 344 x Brown Norway F1 hybrid (FBN) rats were surgically implanted with cannulae targeting BLA, into which pAAV-CaMKIIa-eNpHR3.0-mCherry (halorhodopsin) was delivered, and optic fibers were cemented. Rats were subsequently trained on an adjustable delay, intertemporal choice task in which preference for small vs. large rewards was evaluated in presence of increasing delays to large rewards. Upon reaching stable baseline performance, light-induced BLA inactivation was performed during deliberation (the period before choice) and outcome (after reward delivery). To control for effects of repeated laser stimulation on choice behavior, in other sessions, rats received discrete light-induced inactivation only during intertrial intervals (ITIs). In comparison to baseline and ITI, discrete BLA inactivation during deliberation

increased young and aged rats' choice of the large, delayed reward, thus producing a pattern of choice performance in young that mimics that of aged rats. In contrast, BLA inactivation during the small reward outcome decreased choice of the large, delayed reward in young rats only. In a second cohort of behaviorally naïve young and aged FBN rats, total RNA was extracted from the BLA, and RT-qPCR was used to assess basal expression of genes involved in glutamatergic and GABAergic signaling. GABAB receptor transcripts were reduced in the aged BLA, suggesting this brain region undergoes molecular changes to inhibitory signaling in aging. Finally, in a third cohort, young FBN rats were surgically implanted with cannulae targeting the BLA. Acute infusions of the GABAB receptor agonist, Baclofen, decreased choice of the large delayed reward in a dose-dependent manner. Together, these findings suggest that age-associated shifts in BLA excitatory/inhibitory signaling attenuate the influence of incentive motivation on cost-benefit decision making and contribute to the enhanced ability of older subjects to delay gratification.

17. If you give a rat a coffee…: Investigating the effects of caffeine on the cognitive and emotional response in Long-Evans male rats. Perdomo-Trejo, Jose; Scarola, Samantha; Granger, Megan; Gerecke, Kim; Bardi, Massimo; Department of Behavioral Neuroscience, Randolph-Macon College, Ashland, VA. The neuroprotective properties of caffeine have been widely noted in epidemiological studies. Rodent models of neurodegenerative disorders have found caffeine to prevent d-galactose-induced effects and partial protection from 1-methyl-4-phenyl-1,2,3,6 tetra-hydropyridine (MPTP) neurotoxicity. However, there exists a paucity of research investigating the neuroprotective effects of caffeine in non-disease aging models. Accordingly, the goal of the current study was to further investigate the cognitive, emotional, and physiological consequences of administrating caffeine throughout the lifespan of healthy male Long-Evans rats. Starting at 21 days of age, adult male Long-Evans rats were administered different doses of caffeine 3 times/week: control (saline injection), low caffeine dose (25 mg/kg), and high caffeine dose (50 mg/kg) (n=10 per group). The animals' behavior was observed for changes in locomotion and anxiety-like behaviors following treatments. At one and seven months of age, the animals were exposed to two behavioral tasks, a variable cognition task (persistence test/novel object) and an emotional assessment task (forced swim test). Fecal samples were collected to throughout the study to assess biomarkers of stress and emotional resilience such as corticosterone (CORT), dehydroepiandrosterone (DHEA), and testosterone (T). Results indicate that the average weight of the animals significantly decreased with higher doses of caffeine. Results of the behavioral observations indicated the high caffeine dose treatment group showed a significantly higher anxiety (lower assisted reared and higher grooming interrupted levels) than both the control and low dose treatment group. Analysis of the variable cognitive tasks are still preliminary. Hormonal assays for CORT and DHEA indicated levels of both hormones were significantly higher in the high dose treatment group as well. Furthermore, CORT to DHEA ratio, a measure of allostatic load, was significantly higher in the high caffeine dose treatment group at baseline, but was not significantly different after an ecologically relevant and stressful task. This may indicate a dose dependent synergistic relationship between CORT and DHEA in times of high stress. These results provide support for the claimed weight loss benefits of caffeine. At nine months of age, brain sections will be stained for Iba-1 and GFAP to reveal microglia and astrocytes, respectively, to investigate the neuroprotective effects of caffeine.

18. Individual differences in cholinergic modulation of 22kHz distress vocalizations in rats during fear conditioning and extinction. Devin M. Kellis[1], Kris F. Kaigler[1], & Marlene A. Wilson[1] 1Department of Pharmacology, Physiology, and Neuroscience; University of South Carolina School of Medicine. Post-traumatic stress disorder (PTSD) develops in some, but not all, individuals after traumatic experiences, suggesting that neurobiological factors may confer resiliency, or risk, to the long-term negative effects of traumatic stressors. Our laboratory has demonstrated that outbred Long-Evans rats show individual differences in conditioned fear behaviors, particularly during extinction of cue-induced freezing behavior following fear conditioning, suggesting that this strain may serve as a useful model for characterizing the neurobiological mechanisms that underlie differential responses to traumatic stress. The cholinergic system may be of particular importance for stress-related

disorders as it mediates attention to environmental cues and provides neuromodulatory input to brain regions that regulate conditioned fear and fear extinction. We hypothesized that in addition to individual differences in freezing behavior during fear extinction, rats would also display differences in 22 kHz ultrasonic distress calls during the acquisition of conditioned fear or fear extinction, and that these vocalizations would be modulated by administration of the muscarinic acetylcholine receptor antagonist scopolamine (SCOP). Therefore, we recorded 22 kHz ultrasonic vocalizations (USVs), which are often emitted by rats during aversive situations, as well as freezing behavior during fear acquisition, re-exposure to the context, recall of cue-conditioned fear, cue extinction, and cue generalization. Scopolamine (SCOP, 1.0 mg/kg, ip) was given 30 min prior to extinction or cue-conditioned recall to examine effects on freezing behavior and 22 kHz USVs. We found that rats exhibiting highest freezing behavior and poor cued fear extinction showed more 22 kHz USVs (higher number and longer total duration) during acquisition, cue-conditioned recall, extinction, and tone generalization trials compared to the low freezing rats. SCOP before cue-conditioned recall attenuated USVs during extinction learning and extinction recall, which is consistent with studies demonstrating a relationship between cholinergic (muscarinic) activation and the emission of 22 kHz USVs. We speculate that muscarinic receptors may play a role in extinction learning related to 22 kHz distress vocalizations and SCOP might blunt negative affective processing during re-exposure to conditioned cues.

19. Disrupting Tip60 improves systems consolidation through effects on H2A.Z. Klotilda Narkaj[2], Amber Azam[2], Gilda Stefanelli[1], Firyal Ramzan[1], Alexandria Angco[1], Karina Servado[1], Iva B. Zovkic [1,2] 1Department of Psychology, University of Toronto Mississauga, 2Department of Cell and Systems Biology, University of Toronto. Memory formation is a protracted process that initially involves the hippocampus and becomes increasingly dependent on the cortex as the memory ages. Existing research has implicated stable changes in DNA methylation as a contributor to this process, whereas changes in histone modifications are typically found to be transient. Here, we investigated whether histone H2A.Z, a newly identified epigenetic regulator of learning and memory, is stably modified in the hippocampus and the cortex at delayed time points after learning. Mice were exposed to contextual fear conditioning and brains were collected either 24 hours or 30 days after learning. Using chromatin immunoprecipitation, we quantified H2A.Z and acetylated H2A.Z (AcH2A.Z; a positive marker of transcription) binding on memory-related genes. After 24h, we observed increased levels of H2A.Z acetylation on immediate early genes in fear conditioned mice in the hippocampus, demonstrating the persistence of this epigenetic modification beyond the initial consolidation window (up to 6h). 30 days after training, we detected lasting changes in both H2A.Z binding and H2A.Z acetylation in the medial prefrontal cortex (mPFC), particularly on synapse-related genes. Previously, we showed that H2A.Z in both the hippocampus and the cortex is transiently modified after learning. Here, we show that H2A.Z is stably regulated, but that this regulation is gene-specific, such that changes associated with immediate-early genes are no longer evident at 30 days, whereas, changes associated with synaptic genes persist to support memory maintenance.

20. Enhancing effects of acute exposure to cannabis smoke on working memory performance Blaes Shelby L.[1], Orsini, Caitlin A.[1], Stubbs, Toneisha D.[1], Ferguson, Shandera N.[1], Heshmati, Sara C.[1], Bruner, Mathew M.[1], Wall, Shannon C.[1], Febo, Marcelo[1,2,4], Bruijnzeel, Adriaan W[.1,2,4], Bizon, Jennifer L.[1,2,4], Setlow, Barry[1,2,3,4] Departments of Psychiatry1, Neuroscience2, Psychology3, Center for Addiction Research and Education4, University of Florida, Gainesville, FL. Cannabis is the most widely used illicit drug in the United States and worldwide, and cannabis use is reported to cause cognitive impairments. Given that the primary route of cannabis use in humans is through smoking, however, there is comparatively little research in animal models that has investigated this route of administration. The primary goal of these experiments was to determine how acute exposure to cannabis smoke affects performance in a delayed response working memory task in rats. A secondary goal was to determine whether any such effects differ in males and females, as there are reported sex differences in sensitivity to cannabinoids. Adult male (n=15) and female (n=16) Long-Evans rats were trained in a delayed response working memory task. Rats had to remember the location of a response lever over a variable delay

period that ranged from 0-24 s. Smoke exposure began once rats reached stable performance in the task. One hour prior to sessions in the working memory task, rats were placed in a chamber where they were exposed to smoke generated by burning either cannabis (5.3% THC, ~0% CBD) or placebo (0% THC, 0% CBD) cigarettes in an automated cigarette smoking machine. A semi-randomized, within-subjects experimental design was used such that, each rat was exposed to smoke from 0, 1, 3, and 5 cigarettes of each type, with at least a 48 h washout period between successive exposures. Subsequent experiments evaluated the effects on working memory performance of acute administration of THC (0, 0.3, 1.0, 3.0 mg/kg) and the CB1 receptor antagonist rimonabant (0, 0.2, 0.6, 2.0 mg/kg). Prior to smoke exposure sessions, male rats performed more accurately than females on the working memory task. Analysis of performance in females revealed no effects of estrous cycle. Exposure to smoke from cannabis cigarettes had no effects on working memory accuracy in males, but significantly and dose-dependently enhanced accuracy in females. Acute exposure to placebo smoke had no effects on performance in either sex. Initial data suggest that acute administration of the highest doses of both THC and rimonabant tended to impair performance in both sexes. The results of these experiments suggest that passive exposure to cannabis smoke can enhance performance on a working memory task. The fact that this effect was evident only in female rats is consistent with evidence that females are more sensitive than males to the behavioral effects of cannabinoids. The absence of these enhancing effects following placebo smoke exposure suggests that smoke itself was not the cause of the enhanced performance. Ongoing experiments will determine whether enhancing effects of cannabis smoke on working memory are mediated through CB1 receptors, and whether these effects are evident in other forms of cognition.

21. Effort-related decision making in humanized COMT mice: Effects of Val158Met polymorphisms and dopamine antagonism. Jen-Hau Yang[1], Rose Presby[1], Suzanne Cayer[1], Renee Rotolo1, R. Holly Fitch[1], Merce Correa[1,2], John Salamone[1]. 1Behavioral Neuroscience Division, Department of Psychology, University of Connecticut, Storrs, CT, USA, 2Dept. of Psychobiology, University of Jaume I, Castelló, Spain. Catechol-o-methyltransferase (COMT) is an enzyme that metabolizes catecholamines, and is crucial for the clearance of dopamine (DA) from the prefrontal cortex. Val158Met polymorphism, causing a valine (Val) to methionine (Met) substitution at codon 158, has been shown to be associated with schizophrenia and depression. Although studies investigating the relation between Val158Met polymorphisms and depressive symptoms have yielded inconsistent findings, several reports indicate that negative symptoms in schizophrenics (such as loss of motivation, social withdrawal etc.) are associated with the Val allele. In the present study, three COMT genotypes (wild-type (WT), Val, Met) of mice were tested using an effort-related decision task conducted in touchscreen operant boxes. The mice were trained to choose between delivery of a preferred liquid diet that reinforced panel pressing on various fixed ratio (FR) schedules (high-effort alternative), or intake of pellets that were concurrently available in the box (low-effort alternative). Panel press response requirements were controlled by varying the FR level (FR1, 2, 4, 8, 16) in an ascending and descending sequence across weeks of testing. There was no significant group difference in initial touchscreen operant training, suggesting that all three genotype groups were able to acquire the task. Behavioral results show an inverse relationship between the number of reinforcers delivered by panel pressing and pellet intake across the different FR levels in all three groups. Also, there was a significant group x FR level interaction, with panel presses in the Val group being significantly lower than WT group on FR8. Moreover, the effects of the DA D2 receptor antagonist haloperidol were assessed in mice responding on the FR2 and FR4/choice tasks. Haloperidol (vehicle, 0.05, 0.10, 0.15 mg/kg IP) induced dose-related decreases in panel pressing, but did not affect pellet intake. In contrast, reinforcer devaluation by pre-feeding significantly suppressed both panel pressing and pellet intake. These findings indicate that the humanized Val allele in mice modulates performance on the FR/pellet-choice procedure, as marked by lower levels of panel pressing in the Val group when the ratio requirement was moderately high. These studies demonstrate the significance for understanding the contribution of COMT polymorphisms to negative symptoms such as motivational dysfunctions in schizophrenic patients.

22. Change in Environment Leads to a Loss in Spatial Memory and Increases in Depressive-Like Symptoms in Rats. Sumaya, Isabel C.[1] Villarreal, Susie[1]; Hussain, Samirah[1]; Musquez, Morgan[1]; Amick, Charity[1]; Ramirez, Nayeli[1]; Hussain, Anjum[1]; Cabanillas, Irene[1]; Greene, Cassandra[1] 1California State University, Bakersfield, Bakersfield, Ca 93311. The positive impact that enriched environments have on laboratory rodents has been well documented. Namely, rats kept in enriched environments have consistently shown improvement in learning and memory paradigms (Sumaya et al., 2016) and improvement in depressive-like symptoms (Zang at al., 2011). It is clear that enriched environments have a positive impact on both cognitive and emotional domains when animals are provided enrichment, but what is not known is what happens to rodent memory and mood domains when there is a change in environment. To answer this question, we placed 2 month-old male Sprague-Dawley rats (N=40) in either enriched environments (n=20, multilayer: 54cm L x 89cm H x 82cm W: toys, tunnels, chew bones, chew balls, planks) or standard cages (n=20, 43cm L x 20cm H x 23cm W) for 6 months. After the six-month period we reversed the housing of half the rats placing rats that were originally in enriched environments in standard cages (EESC) for one month and rats in standard cages in enriched environments (SCEE) for one month. We also maintained a control group where rats where kept in their original housing (Standard Cages: SCSC & Enriched Environments: EEEE). After the one-month period of reversal we measured performance in the 8-arm radial maze (spatial learning) and the forced swim test (depressive-like symptoms). In the domain of memory, the rats that were kept in their original enriched environments experiencing no reversal (EEEE), as expected, showed the best memory with the least amount of errors as averaged over the 8 days in the 8-arm (EEEE 1.36+0.3). In reversing the environment from enriched to standard housing (EESC) rats showed an increase in errors in the 8-arm maze (1.97 +0.35 errors) as compared to their control counterparts. For the animals that were housed in standard cages then placed in enriched environments (SCEE), they experienced the greatest amount of errors (2.65+0.53 errors) showing no positive effects of the reversal as compared to their control counterparts that were kept in their standard cages (SCSC: 2.21+0.29 errors). In the domain of depression, the rats that were kept in their standard cages (SCSC) experienced the greatest amount of immobility in the forced swim test showing the highest levels of depressive-like symptoms (179.80 +12.25 sec). Conversely, the rats the were kept in their enriched environments (EEEE) showed the least amount of depressive-like symptoms (95.80 +15.56 sec). In reversing the environments, the SCEE group, experienced a decrease in depressive-like symptoms (112 +8.19 sec), while the EESC groups experienced an increase in depressive-like symptoms (156.33 +12.33 sec). These results provide first time data that a change in environment from enriched to standard housing can negatively impact learning and memory and depressive-like symptoms in rodent models. This research was supported by the National Institutes of Health General Medical Sciences (NIHGMS) (NRSA) T34 GM118212 and the Gayle and Ben Batey Neuroscience Fund.

23. Fluoxetine, but not scopolamine, requires BDNF induction in the medial prefrontal cortex to mediate antidepressant effects. Nicole La Grange[1], Marcia Ramaker[1], Stephanie Dulawa[1]. 1University of California San Diego. Brain-derived neurotrophic factor (BDNF) induction in the hippocampus and/or medial prefrontal cortex (mPFC) is considered a hallmark of antidepressant onset. Upregulation of BDNF expression has been shown to be necessary for the antidepressant effects of classical antidepressants, and the rapid-onset antidepressant ketamine. However, the effect of fast-onset antidepressant scopolamine on BDNF levels is not well established. We assessed whether BDNF induction in the mPFC was required for fluoxetine or scopolamine to mediate antidepressant behavioral effects in the chronic forced swim test (cFST). We first tested scopolamine for its antidepressant-like effects in two tests of antidepressant onset, the chronic forced swim test and novelty induced hypophagia test. Next, we performed region-specific knock down of BDNF by infusing a cre recombinase-expressing adeno-associated virus into the mPFC of BDNF floxed mice, and then determined the antidepressant-like effects of either scopolamine or fluoxetine in the cFST. In normal mice, one day of continuous (dose) scopolamine treatment produced antidepressant-like effects in the NIH test and the cFST, while previous work has shown that 2 weeks of chronic fluoxetine treatment are required for these effects. Furthermore, knockdown of BDNF in the mPFC prevented the antidepressant effects of chronic fluoxetine treatment, but not one day of

scopolamine treatment, in the cFST. These results indicate that scopolamine may be unique among known antidepressants in not requiring induction of BDNF expression in the mPFC to exert antidepressant behavioral effects. Our findings reveal a key mechanistic difference between the antidepressant effects of scopolamine compared to classical antidepressants and ketamine.

24. Effects of the serotonin transport inhibitor fluoxetine on effort-related decision making in male and female rats. Rotolo, Renee[1], Yang, Jen-Hau[1], Presby, Rose[1], Correa, Merce[1,2], Salamone, John D[1] 1Department of Psychological Sciences, University of Connecticut, 406 Babbidge Road, Storrs, CT, USA, 06269-1020, 2Psychology, Univ. Jaume I, Castelló, Spain. Major depressive disorder is characterized by a multitude of behavioral, cognitive, and mood-related symptoms. In addition, motivational symptoms such as anergia, psychomotor retardation, and fatigue are common facets of depression. These motivational symptoms are highly resistant to treatment with commonly prescribed drugs such as serotonin transport (SERT) inhibitors. While catecholamine uptake inhibitors such as bupropion (Wellbutrin) have been reported to be somewhat effective for treating the psychomotor/motivational symptoms of depression, SERT inhibitors such as fluoxetine (Prozac) and citalopram (Lexipro) are relatively ineffective, and can actually induce or exacerbate these symptoms. Our laboratory has developed behavioral tasks that allow rats to choose between high-effort alternatives that lead to more highly valued rewards, and low-effort alternatives that lead to less valued rewards. Depressed people show a low-effort bias in human tests of effort-related decision making, and animal studies show that conditions associated with depression can induce changes in effort-based choice. For example, rats treated with the vesicular monoamine transport inhibitor tetrabenazine, which induces or exacerbates symptoms of depression in humans, can alter effort-related choice, reducing selection of the high effort alternative. The SERT inhibitors fluoxetine and citalopram fail to reverse the effort-related effects of tetrabenazine, and in fact tend to exacerbate them. Additional research has shown that fluoxetine alone suppresses high-effort lever pressing in both males and females in the dose range of 5.0-15.0 mg/kg. Ongoing studies are examining the ability of 5-HT2A and 5-HT2C receptor antagonists to reverse the fluoxetine-induced motivational impairments. Elucidating the roles of these particular serotonin receptors could lead to a greater understanding of the neurochemical mechanisms that regulate effort-related aspects of motivation, and ultimately, could foster the development of possible treatments that augment the therapeutic efficacy of serotonin uptake inhibitors.

25. The role of corticotropin-releasing factor signaling in depression-related cognitive impairments under conditions of uncertainty. Courtney A Bryce[1], Alexandra J Adalbert[1], Mona M Claes[1], Stan B Floresco[1]. 1University of British Columbia. Depression is a stress-related disorder characterized by a debilitating constellation of affective and cognitive symptoms. Though the etiology of depression is currently unknown, depressed patients show potentiated corticotropin-releasing factor (CRF) levels. Animal models of depression and CRF application in vitro produce alterations in dopamine (DA) neuron activity, demonstrating a potential role for CRF, perhaps via DA signaling, in mediating depressive symptoms. Indeed, in preclinical experiments, CRF administration produces a depressive-like phenotype in both simple and complex assays, indicating a possible role for CRF in dysphoric and amotivational symptoms of depression. Typically, the adverse outcomes associated with depression are due to affective symptoms, however, depression also causes substantial cognitive impairments. Therefore, our aim was two-fold: 1) to elucidate the potential role for CRF on a battery of complex tasks in which depressed patients demonstrate cognitive impairments, including cognitive flexibility and risk/reward decision-making, and 2) to clarify the actions of central CRF administration on VTA DA neuron physiology in vivo. To this end, we centrally administered CRF prior to training and following extensive training on a probabilistic reversal learning task. In this task, one lever is designated as 'correct' (80% reinforced) and the other lever is 'incorrect' (80% non-reinforced). After 8 consecutive correct choices, reward contingencies are reversed. CRF in this task facilitated cognitive flexibility, increasing reversals by increasing reward sensitivity and reducing negative feedback sensitivity when animals received extensive training, whereas reward sensitivity and negative feedback sensitivity were both reduced when CRF was administered at acquisition. Additionally, CRF improved decision-

making when risk/reward information was internally represented, increasing choice of the more rewarding, but riskier, option when odds were good and reducing choice when odds were poor. However, when external cues guided choice behavior, CRF impaired decision-making, increasing choice of the more rewarding, but riskier, option when odds were poor. Collectively, these results reveal the complex effects of CRF on various aspects of cognition, some of which mirror those in depression. Future experiments will investigate the role of CRF on DA neuron activity in vivo to learn how CRF and DA might interact to mediate cognitive alterations.

26. Effects of chemogenetic inhibition of dopamine transporter- or A2A-expressing neurons on spontaneous activity and motivation to consume a palatable food reward. J. Wherry, J.D Jentsch. State University of New York at Binghamton, Department of Psychology, 440 Vestal Parkway East, Binghamton, NY, 13902, USA. Dopamine (DA) transmission in the striatum influences the motivated pursuit of rewarding stimuli. Pharmacological and opto- and chemo-genetic studies have suggested that the release of DA onto D2+/A2A+-expressing striatopallidal neurons, plays a role in this process. To determine the potentially dissociable roles of DA-releasing ventral midbrain and striatopallidal neurons on motivational processes, we employed double transgenic mice that expressed inhibitory DREADDs - designer receptors that are activated only by otherwise inert ligands - only in dopamine transporter (DAT) or A2A adenosine receptor (A2A) expressing neurons, allowing us to transiently inhibit either DA-releasing neurons (DATcre/DREADD) or striatopallidal neurons (A2Acre/DREADD) during various tests. In the first experiment, locomotor activity in a familiar environment was measured after mice received an injection of the DREADD ligand CNO (1 or 2.5 mg/kg) or vehicle. Both lines of mice exhibited decreases in spontaneous activity in response to the high dose of CNO. Second, voluntary consumption of sweetened condensed milk (SCM) was assessed. Both doses of CNO caused a significant decrease in SCM consumption in A2Acre/DREADD, but not DATcre/DREADD, mice. Finally, mice were trained and tested on a progressive ratio task, wherein increasing numbers of lever presses were required to obtain access to SCM. We found that CNO and Compound 21 (3 mg/kg) reduced active lever pressing in A2Acre/DREADD mice but not DATcre/DREADD mice. In none of these experiments were effects of CNO or Compound 21 detected in littermate control mice that were not double transgenic, supporting the idea that the effects observed were not due to back metabolization of CNO. Thus, inhibition of A2A-expressing (presumably striatopallidal) neurons suppresses free and effortful reward pursuit and consumption; the degree to which this is attributable solely to impaired motor activity requires further study. Further studies will also assess the opposite effects of activating these same neural populations using excitatory DREADD (Gq) construct. Overall, these data do not support the idea that dopaminergic neural activity plays a major role in motivation for a palatable reward, but does implicate A2A-expressing neurons in both motor and motivational phenotypes.

27. Reward motivation in humans and its relationship to dopamine $D_{2/3}$ receptor availability: A pilot study with dual [^{11}C]-raclopride and [^{11}C]-(+)-PHNO imaging. Fernando Caravaggio[1,2], PhD, Gagan Fervaha[2], PhD, Caleb J. Browne[3,4], PhD, Philip Gerretsen[1,2], MSW., M.D., PhD, Gary Remington[1,2], M.D., PhD, Ariel Graff-Guerrero[1,2], M.D., PhD. 1Research Imaging Centre, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario, Canada, M5T 1R8. 2Department of Psychiatry, University of Toronto, 250 College Street, Toronto, Ontario, Canada, M5T 1R8. 3Department of Psychology, University of Toronto, 250 College Street, Toronto, Ontario, Canada, M5T 1R8. 4Section of Biopsychology, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario, Canada, M5T 1R8. Rodent studies suggest that DA signaling at $D_{2/3}$R receptors ($D_{2/3}$R) in the ventral striatum (VS) is critical for reward motivation. Whether this is also true in humans is unclear. Positron emission tomography (PET) studies in healthy humans have generally not observed a relationship between $D_{2/3}$R availability in the VS and motivation. We developed the “Mounting-Effort for Reward Task” (MeRT) to assess high motivational demand for, i) gaining money (%CS+), ii) losing money or avoiding electric shock (%CS-), and, iii) no reward (%Neutral). Receipt was contingent on participants making sufficient button responses relative to a “reward-threshold” determined by prior motor performance. This reward-threshold was dynamically increased if surpassed, making the task increasingly more difficult on every trial. The MeRT was preliminary validated in 29

healthy volunteers (mean age: 25.83±3.58; 15 female). In this sample, %CS+ and %CS- significantly correlated with different dimensions of self-reported apathy. In a sub-sample of 8 healthy volunteers (mean age: 25.75±1.91; 4 female), the MeRT demonstrated good test-retest reliability (%variance: 0.20%-2.61%). Seven healthy male volunteers (mean age: 31.14±5.43) completed the MeRT and provided both [^{11}C]-raclopride and [^{11}C]-(+)-PHNO PET scans to assess $D_{2/3}$R availability. %CS+ and %CS- were positively correlated with [^{11}C]-raclopride binding in the dorsal striatum. %CS+, %Cs-, and %Neutral were positively correlated with [^{11}C]-(+)-PHNO binding in the globus pallidus. Thus, increased expression of D_2R in the dorsal striatum, and D_3R in the globus pallidus, may be related to motivation for rewards. Larger PET studies are required to formally validate the MeRT and replicate our pilot findings.

28. Glutamatergic mechanisms in the inferior colliculus play a key role in paradoxical kinesia induced by appetitive 50- kHz ultrasonic vocalisations in rats. Luan Castro Tonelli[1], Markus Wöhr[1], Rainer K. W. Schwarting[1], Liana Melo-Thomas[1]. 1 Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, Gutenbergstrasse 18, 35032 Marburg, Germany. Immobile parkinsonian patients may be able to make quick movements, when excited by external stimuli. This is a phenomenon called paradoxical kinesia (PK) which refers to a sudden transient ability of akinetic patients to perform motor tasks they are otherwise unable to perform. The mechanisms underlying this phenomenon are unknown. However, in a previous study we proposed a new animal model to investigate PK in akinetic rats using species-relevant signals, namely rat ultrasonic vocalizations (USV) which are typical for social situations with positive valence like juvenile play or sexual encounters. Our aim in the present study was to uncover underlying brain mechanisms of PK. We focused on the inferior colliculus (IC) since it not only serves as an acoustic relay station, but can also modulate haloperidol-induced catalepsy. To test the role of the IC in PK induced by 50-kHz USV, male rats received intracollicular administration of NMDA (30nmol) or diazepam (10µg or 20µg) or its respective controls 10 min before haloperidol (0.5 mg/kg; ip). Rats were exposed to playback of 50-kHz USV, white noise, background noise or silence, 10 min each with 5 min intervals. The catalepsy test was measured during the bar test, which consists of placing the rat with its forepaws on a horizontal bar. The time until it stepped down was measured (maximum 600s). In animals which had received saline or vehicle microinjections into the IC, playback of 50-kHz USV significantly reduced haloperidol-induced catalepsy, and no such effects were observed in the case of other stimuli. However, the intracollicular administration of NMDA prevented the playback of 50-kHz USV effect on haloperidol–induced catalepsy. In contrast, although intracollicular diazepam microinjection potentiated the haloperidol-induced catalepsy, it did not affect the response to 50-kHz USV. Therefore, although both drugs microinjected into the IC potentiated haloperidol-induced catalepsy, they differ in their response to the 50-kHz USV playback. The agonist (NMDA) suppressed the effectiveness of the 50-kHz playback whereas the microinjection of the agonist GABA (diazepam) did not prevent the PK induced by the 50-kHz playback. These findings suggest that the neurobiological mechanisms underlying PK through the IC may be rather glutamatergic than GABAergic. Our approach to studying PK might be useful for uncovering the mechanisms behind this phenomenon and improving behavioural therapies for Parkinson's disease.

29. Adolescent oxytocin treatment alters anxiety-like behaviour elicited by early life stress differently depending on sex. Sarah Baracz, Harry Carey, Katherine Robinson, Anita Turner, Nick Everett, Jennifer Cornish. Macquarie University, NSW, Australia. Exposure to early life stress (ELS) is associated with an increased vulnerability for mental health disorders later in life. Animal studies have shown that ELS alters the oxytocin and neuroendocrine stress systems, which contributes to the development of anxiety-like and depressive-like behaviours that endure into adulthood. Recently, oxytocin administration in adulthood was shown to reduce the depressive-like behaviours caused by ELS. However, oxytocin administration during adolescence, one of the system's critical developmental periods, has not been investigated. Considering this, the aim of our study was to determine whether an adolescent oxytocin treatment regime could reverse the anxiety-like effects and cellular changes in hypothalamic oxytocin and corticotropin-releasing factor (CRF) neurons that are produced by ELS. Long Evans

pups underwent maternal separation for either 15 or 360 mins on postnatal days (PND) 1 to 21. During adolescence (PNDs 28-42), rats received a daily injection of either oxytocin (1mg/kg; ip) or saline. In adulthood (between PND 60-65) rats were exposed to the open field paradigm to measure anxiety-like behaviour. Brains were collected two hours later for immunofluorescence. Coronal sections containing the paraventricular and supraoptic nuclei were stained for oxytocin and CRF cell bodies. Our results from the open field showed that ELS in males and females increased frequency of low leaning behaviour, which correlated with decreased time spent in the centre of the apparatus. This is indicative of increased anxiety. Additionally, oxytocin treatment in stressed males reduced low leaning, and increased time engaging in high leaning, which correlated with more time spent in the outer central area, suggesting a reduction in anxiety. In females, oxytocin treatment reduced low leaning in the non-stressed controls, and increased high leaning in both the stressed and non-stressed groups. Results from the immunofluorescence analysis will also be discussed. Overall, these findings suggest a role for adolescent oxytocin treatment in reducing the impact of ELS on novel ethological measures of anxiety-like behaviours, which differs depending on sex.

30. Drd3 signaling in the lateral septum mediates early life stress-induced social dysfunction. Sora Shin[1], Horia Pribiag[1], Varoth Lilascharoen[1], Daniel Knowland[2], Xiao-Yun Wang[1], Byung Kook Lim[1,2,3] 1Neurobiology Section, Biological Sciences Division, University of California, San Diego, La Jolla, California, USA. 2Neurosciences Graduate Program, University of California San Diego, La Jolla, California, USA. 3Biomedical Sciences Graduate Program, University of California San Diego, La Jolla, California, USA. Children exposed to adverse experiences (e.g., physical abuse, emotional neglect, etc.) during a critical period in their development are more likely to have social dysfunction later in life. Those experiences, collectively referred to as early life stress (ELS), can induce psychiatric symptoms associated with diseases like autism spectrum disorder (ASD), schizophrenia, and major depression. Little is known, however, about the relevant molecular signaling within a specific neural substrate that governs ELS-induced social dysfunction. Here, we identify dopamine receptor 3 (Drd3)-expressing-LS (Drd3LS) neurons as a critical component mediating the detrimental effects of ELS on social behavior. Employing an early social deprivation (ESD) stress paradigm, we found that Drd3 signaling in the LS is significantly down-regulated in mice exposed to ESD stress, and that this is accompanied by abnormal social behaviors such as reduced social preferences and severe communication deficits. Using in vivo Ca2+ imaging, we found that social stimuli produce significantly less activity in Drd3LS neurons of ESD mice than in controls. Notably, optogenetic activation of Drd3LS neurons rescues this ESD-induced social impairment. Pharmacological treatment with the Drd3 agonist PD128907, which increases the activity of Drd3LS neurons, also normalizes the abnormal social behaviors of ESD mice. Taken together, our findings identify Drd3 signaling in the LS as a critical mediator of the ELS-induced social impairments in adulthood. Drd3 in the LS may therefore constitute an important therapeutic target for the treatment of the severe social impairments commonly observed in numerous neuropsychiatric disorders.

31. Role of Cannabinoid CB1 receptors in mediating the long-term effects of adolescent chronic stress on the behavioral impairments following traumatic brain injury in adult rats. de la Tremblaye, Patricia B.[1]; Wellcome, Jody L[1].; Wiley, Kaitlyn M[1].; Cheng, Jeffrey P[1].; Bondi, Corina O[1]., Kline, Anthony E[1]. 1 Physical Medicine & Rehabilitation and Safar Center for Resuscitation Research, University of Pittsburgh, Pittsburgh, PA. Endocannabinoids are involved in the adaptation of the brain's response to stress through cannabinoid type 1 (CB1) receptors. CB1 activation has also been implicated in the neuropathology of traumatic brain injury (TBI), and has shown promise as a potential therapeutic target. However, it is unknown whether CB1 activation can reverse the long-term effects of adverse stress exposure during adolescence on adult TBI emotional and cognitive recovery. In the current study, adolescent male Sprague-Dawley rats were exposed to 4 weeks of chronic unpredictable stress (CUS) on postnatal day (PND) 30-60. After an additional 4 weeks of resting (PND 60-90), rats were anesthetized and receive either a controlled cortical impact of moderate severity (2.8 mm tissue deformation at 4m/s) or sham injury, immediately followed by daily pharmacological treatment with either CB1 agonist, ACEA (1 mg/kg), antagonist, AM251 (2 mg/kg), or vehicle (1 ml/kg), which were administered

intraperitoneally for 7 consecutive days. After this week of recovery, rats were behaviorally assessed for anxiety in the elevated plus maze (EPM) and the open field test (OFT), sociability in the three-chamber social approach test, anhedonia in the sucrose preference test (SPT), and cognitive performance in the novel object recognition (NOR) test, and Morris water maze (MWM). CUS exposure in adolescence increased time spent in the anxiogenic zones of the OFT and EPM and decreased sociability in sham rats, but improved NOR memory, and reduced time to reach the platform in the MWM in both sham and TBI groups, effects which were mediated by CB1 receptors. The results demonstrate that chronic unpredictable stress selectively impairs emotional responses, while providing some cognitive benefits, which may be context-dependent. Furthermore, CB1-mediated neurotransmission may effectively reverse the deleterious effects of adolescent -stress on behavioral recovery post TBI in adulthood.

32. Stress during puberty has differential effects on impulse action and introduction of delays in reward contingencies. González-Martínez, L. F[·1,2], Lee, H. J.[2], Delville, Y[2]. 2 Psychology Department, The University of Texas at Austin. Exposure to stress during childhood and adolescence has a wide range of effects impacting cognition and personality. Thus, early trauma is a risk factor for development of mental disorders during puberty. Our previous studies in hamsters showed that chronic social stress in early puberty results in enhanced impulsive action, in particular decreased action inhibition. In addition, previously stressed animals were found particularly aversive to delays in reward, observed as a rapid inhibition of response rate and interest in rewards. In order to broaden the effects of early stress on impulsive action, we analyzed changes in conditioned responses under varying delays between conditioning cue, addressing the capacity to wait to respond. Male golden hamsters were exposed daily to aggressive adults from postnatal day 28 to 42. Later in adulthood, animals were trained to respond to a light cue by nose-poking into a lid opening that triggered the delivery of food pellets reward in a five-choice-serial-reaction-time task (5-CSRTT). During testing, we introduced random and varying delays (2 to 40 seconds) between the lights in the conditioning chambers and in openings and we looked for premature nose-poking responses as an indicator of impulsive action. As delays grew longer, animals were more likely to perform premature responses. However, previously stressed animals were ca. 25% less likely to perform such actions by the longest delay. There were no significant differences between groups in accuracy, omissions or errors in any of the delays presented. Our results show opposite effects of early social stress on the two components of impulsive action: decreased action inhibition, but enhanced capacity to wait for a response. Our results also show differential responses to introduction of delays in the contingencies of reward: enhanced tolerance to delays between conditioning cues, but decreased tolerance for reward delays after a response. These studies while indicating complex neural changes underlying these behavioral consequences may help explaining the diverse patterns of impulsivity in personality disorders associated with early stress. These studies also point to early stress as a predictor of patient adherence to slowly progressing therapies. 1. Supported by predoctoral fellowship from COLCIENCIAS (Colombia).

33. Tracking the impact of early-life challenges on neurobiological correlates of social and stress responses in female adult rats. Kovalev, D., Brooks, M., Kent, M., & Lambert, K. Dept. of Psychology, University of Richmond, VA 23173. In humans, poverty and unpredictable environments have been associated with negative socioemotional developmental outcomes (Blair et al., 2016). Accordingly, the current study utilized a rodent model to assess the effects of restricted resources and unpredictable threats [simulating a poverty/low socioeconomic status (SES) model] on socioemotional neurobiological functions. In this model, female rats were raised in four different conditions defined by availability of materials for nest building [standard and restricted resources for control (CON) and low SES groups] and presence or absence of threat (predator odors) throughout the lactation period. Following weaning, offspring were pair-housed [according to their group assignments LOW SES/no threat; LOW SES/threat; CON SES/no threat; CON SES/threat, n=8 each group] in standard housing conditions for one year. Adult offspring were assessed in a social interaction task with a novel male rat and cage mate confined in a plastic container. Prior to the social task, rats were habituated to the arena to observe anxiety responses in a novel

environment. Following behavioral testing, the brains were assessed for oxytocin (associated with social responsiveness). Behavioral results indicated that, during habituation, animals exposed to threat (T) exhibited higher rearing responses (p=.012; exploratory behavior). When a cage mate was placed in a plastic container, no threat (NT) animals exhibited more digging behavior (p=.03); threat animals exhibited more rearing behavior (p=.008). When a novel male rat was placed in a plastic container, animals exposed to threat exhibited fewer responses directed toward the male (p=.009) as well as escape attempts from the cage (p=.021), yet they exhibited increased bouts of interrupted grooming (p=.007). Further, LOW SES animals exhibited more escape behavior (p=.017). A significant T/SES interaction indicated that rats raised in CON SES/NT conditions exhibited more nose-to-nose contact with the novel male (p=.021). Histology data revealed nonsignificant trend indicating increased oxytocin immunoreactivity in the supraoptic nucleus in no threat animals (p=.081). To assess stress responsiveness, corticosterone levels were measured. LOW SES/T condition rats exhibited the highest levels of corticosterone (p<.0005). In sum, behavioral and neurobiological data suggest long-term socioemotional effects in adult animals exposed to stressful conditions during the limited time of lactation.

34. Role of HDAC2 in the treatment for schizophrenia and epilepsy. Daisuke Ibi[1,2,3], Mario de la Fuente Revenga[3], Masayuki Hiramatsu[1], Javier González-Maeso[2,3] 1Department of Chemical Pharmacology, Meijo University, Nagoya, 468-8503, Japan. 2Department Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA. 3Department of Physiology and Biophysics, Virginia Commonwealth University, School of Medicine, Richmond, VA, 23298, USA. Histone deacetylases (HDACs) represses gene transcription through removal of acetyl groups from histone tails. Although HDAC2 plays a crucial role in expression of various genes involved in neuronal function, its validity as a therapeutic target of brain diseases such as schizophrenia and epilepsy remains unknown. In this study, we investigated the role of HDAC2 in the treatment for these diseases. The schizophrenia symptoms fall into psychosis and cognitive dysfunction. Although chronic antipsychotic treatment produces significant reduction of psychosis, cognitive deficits in schizophrenics do not improve upon antipsychotic treatment; some patients even deteriorate. This underlines the need to improve treatment for schizophrenia. Here, we demonstrated that chronic treatment of antipsychotic up-regulated HDAC2 expression in the mouse frontal cortex. Further, chronic antipsychotic treatment impaired cognitive function in the novel object recognition test, which was not observed in forebrain-specific HDAC2 conditional knockout (HDAC2-cKO) mice, suggesting that HDAC2 up-regulation upon antipsychotics may interfere with treatment for cognitive deficit in schizophrenics. Next, we focused on epilepsy, a common and refractory neurological disorder, in which brain-derived neurotrophic factor (BDNF) plays a causative role because of BDNF-evoked neuronal abnormal excitation in the hippocampus. Valproic acid (VPA) that stimulates GABA, an inhibitory amino acid, signaling is one of the most widely used as an anti-epileptic drug. Interestingly, VPA is also known as an inhibitor to HDACs but contribution of HDAC inhibition to anti-epileptic effects remains unknown. We found that pre-treatment of HDAC inhibitors such as sodium butyrate significantly suppressed epileptic seizure in kindling mouse model continuously treated with pentylenetetrazol (PTZ). Further, hippocampal BDNF up-regulation and epileptic seizure in kindled mice after continuous PTZ treatment were absent in HDAC2-cKO mice. Given that HDAC2 epigenetically affects BDNF expression, inhibition of HDACs including HDAC2 could suppress epileptic seizure through the control of BDNF expression. Together, HDAC2 may be available as a therapeutic target to improve the treatment for brain diseases such as schizophrenia and epilepsy.

35. Effects of Cacna1c Haploinsufficiency on Social Interaction Behavior and 50-kHz Ultrasonic Vocalizations in Rats. Tobias M. Redecker, Theresa Kisko, Moria Braun, Markus Wöhr, Rainer K. W. Schwarting Behavioral Neuroscience, Experimental and Biological Psychology, Philipps-University of Marburg, Gutenbergstr. 18, 35032 Marburg, Germany. The well-established risk gene CACNA1C, especially the rs1006737 allele, was previously associated with a wide range of neuropsychiatric disorders, including autism spectrum disorder (ASD), bipolar disorder (BPD), posttraumatic stress disorder (PTSD), and schizophrenia (SCZ). Remarkably, deficits in social functioning are prevalent in all this disorders. The CACNA1C gene encodes an alpha-1 subunit of the

voltage-dependent L-type gate calcium channel Cav1.2, mediating depolarization-dependent calcium influx into the cell. Cav1.2 regulates neuronal excitability, synaptic plasticity and gene expression, and thus plays a fundamental role in brain functioning. In the present study, we used a newly developed genetic rat model to investigate social interaction behavior and 50-kHz ultrasonic vocalizations (USV) in adult female wildtype (+/+) and heterozygous (+/-) Cacna1c rats. Social behaviors, such as sniffing and social grooming, were individually assessed in same and mixed genotype dyads during a 10 minute social interaction period while 50-kHz USV were recorded and subsequently classified in call subtypes. Preliminary results indicate that social behavior is altered in Cacna1c+/- rats compared to their wildtype littermate controls. Most notably, dyads containing Cacna1c+/- rats showed a highly reduced number of pro-social 50-kHz USV. Together, these results indicate that the Cacna1c gene is involved in regulating social behavior and socio-affective communication through 50-kHz USV in rats with relevance for neuropsychiatric disorders, like ASD, BPD, PTSD, and SCZ.

36. Modeling selection of voluntary physical activity in psychiatric disorders: effects of the SSRI fluoxetine in rodents. Rose Presby[1], Bryanna Ye[1], Molly Flynn[1], Renee A. Rotolo[1], Jen-Hau Yang[1], Carla Carratala-Ros[2], Merce Correa[1,2], John D. Salamone[1]. It is important to characterize the factors that influence physical activities such as voluntary exercise in people with psychiatric disorders. Depressed people, on average, show reduced levels of locomotor activity, and it has been suggested that increased physical activity could be a useful therapeutic intervention for some people. Furthermore, many people with major depressive disorder show motivational/psychomotor symptoms such as psychomotor retardation, fatigue, and anergia. Drugs that inhibit the serotonin transporter (SERT inhibitors, also known as SSRIs) are the most commonly used class of antidepressants, however, these drugs have been reported to be relatively poor at treating motivational/psychomotor symptoms, and in some people they can induce or worsen fatigue. In view of this, it is important to develop animal models that assess the factors regulating the selection of voluntary physical activities. The present studies focused on the development of T-maze procedures in rats that allow animals to choose between physical activity (running in a running wheel; RW) vs. intake of a highly palatable food (chocolate). In female Wistar rats, consumption of a highly palatable food was induced by irregular exposure to chocolate in their home cage. Once substantial levels of intake were established, rats were placed in the T-Maze daily for 30 minutes. Ongoing studies examining the effects of the SSRI fluoxetine (Prozac), a common treatment for depression that also reduces appetite, show a drug-induced reduction in both RW activity and chocolate intake. These results are similar to those obtained from mouse studies showing that fluoxetine also suppresses selection of running wheel activity. It is possible that this line of research will contribute to an understanding of the neurochemical factors regulating selection of voluntary physical activity vs. sedentary behaviors, which could be relevant for understanding the role of physical activity in psychiatric disorders.

37. Upregulation of mGlu5 in the basal lateral amygdala and mPFC as a molecular feature of resilience to traumatic stress in rats. Shallcross, John[1], Schwendt, Marek[1], & Knackstedt, Lori[1] 1University of Florida. Post-traumatic stress disorder (PTSD) is a serious mental health condition characterized by increased anxiety, arousal, and impaired fear memory extinction that develops in a subset of individuals exposed to a trauma. To model PTSD in rodents, we exposed a large population of rats to the predator odor 2,3,5-Trimethyl-3-thiazoline (TMT, a component of fox odor) once for 10 minutes and then tested for anxiety 7-21 days later using the elevated plus maze, acoustic startle response, and freezing in the TMT context. We found that following a single exposure to TMT, subsets of both PTSD susceptible and PTSD “resilient” animals emerge out of heterogeneous populations. Following trauma, resilient animals show scores equivalent to non-TMT exposed controls on all anxiety tests, while PTSD rats display high levels of anxiety and increased freezing during re-exposure to the TMT context coupled with enhanced glucocorticoid response. As aberrations in the consolidation and extinction of fear memory in trauma affected individuals and rodents has been linked to abnormalities in cortico-amygdalar circuit activity, we performed quantitative RT-PCR to characterize variability of plasticity associated genes in these regions across phenotypes. Three weeks following TMT or control exposure, RT-qPCR analysis indicated a

significant upregulation of mGlu5 and CB1 receptor mRNA in the amygdala, and upregulation of mGlu5 in the medial prefrontal cortex (mPFC) of resilient animals as compared to both control and PTSD groups. Using fluorescent in situ hybridization (FISH), we found that the concentration of mGlu5 mRNA expression was significantly higher in the basal lateral amygdala (BLA), prelimbic prefrontal cortex (PrL-PFC), and infralimbic prefrontal cortex (IL-PFC) of resilient animals as compared to controls while concentration of mGlu5 mRNA expression in the central amygdala did not differ among the groups. FISH analysis in the BLA indicated increased co-expression of mGlu5 mRNA with glutamate marker vGlut1 mRNA in resilient animals versus controls, however co-expression of mGluR5 mRNA and GABA marker GAD65 mRNA did not differ among the groups. These results show that resilience to traumatic stress may be dependent on the amount of mGlu5 mRNA being expressed in both the PrL-PFC and IL-PFC as well as in glutamatergic BLA neurons.

38. A single injection of losartan improves neurological outcome in male and female rats subjected to ischemic stroke. *Martinez-Jimenez S.M.[1], M. N. Gonzalez-Vega, N.M.[1], Ferchmin, P.A[.2], Martins, A.H.[3]; 1Neuroscience, Universidad Central Del Caribe, Bayamon, PR; 2Biochemistry, Universidad Central del Caribe, Bayamon, PR; 3Phrarmacology, Universidad of Puerto Rico Medical Science Campus, San Juan, PR. Stroke is a leading cause of long-term disability and the leading preventable cause of disability in the United States. Ischemic stroke is caused by a blockade of blood vessels in the brain by a blood clot. The inflammation associated with this blockade causes loss of neurons, astrocytes and increased permeability in the blood brain barrier (BBB). Losartan is an angiotensin type 1 receptor blocker commonly used to decrease blood pressure but also has anti-inflammatory properties and in recent studies, has been observed to help maintain BBB integrity. But these studies have been performed with chronic administration of losartan; the efficacy of a single acute injection of losartan in stroke has yet to be quantified. We propose that a single dose of losartan will decrease the neuronal damage and at least partially restore BBB integrity in male and female rats subjected to ischemic stroke. To verify this hypothesis, we performed middle cerebral artery occlusion (MCAO) to induce an ischemic stroke in male and female Sprague Dawley rats weighing 250-300g. A single injection of losartan (1mg/Kg) or an equal volume of sterile saline was given intravenously as a pre-treatment or post-treatment. Neurological outcome and disability was measured using a modified neurological severity score test (NSS) 24hrs after stroke. NSS is comprised of sensorimotor tests including ability to walk, flexion of limbs, startle reflex, propioreceptive test, motor evaluation and presence of seizures, among others. Failure to preform a task increases the score and a higher score correlates to increased disability. For BBB integrity analysis, 2% Evans Blue (EB) dye was injected and dye infiltration measured inside the brain. Infarct damage was measured using tetrazolium chloride (TTC) solution and determining dead tissue in the brain. Losartan treatment shows a tendency to reduce infarct damage and BBB permeability in both sexes of losartan-treated rats when injected 5 min before stroke. This tendency is replicated in our preliminary data using rats injected 2hrs after the stroke onset. Regardless of injection time losartan treatment significantly improved neurological outcome in both sexes after stroke ($p<0.05$). Therefore, these results suggest that even a single injection conserves the neuroprotective effects of losartan against stroke and could prove to be a useful alternative therapeutic approach in stroke therapy.

39. The role of cannabinoid 2 receptor in modulating microglia activation after a traumatic brain injury. Zamora Maria F[1], Canseco-Alba Ana[1], Liu Qing-Rong2[2], Onaivi Emmanuel S[1], Bierbower Sonya M[1] 1William Paterson University, Wayne, NJ 07470; 2NIA-NIH, Baltimore, MD. Traumatic brain injury (TBI) occurs when a sudden trauma is applied to the head and causes damage to the brain. TBI can result from a multitude of events including most commonly from sports injuries, vehicle collisions, violence, falls, and war. It is estimated that there are 1.4 million cases of TBIs in the USA every year. Injury can result in permanent disabilities and in severe cases it can be fatal. Symptoms after a TBI can be mild, moderate and severe depending on the extent of brain damage as well as location. Long-term behavioral effects can be characterized including depression, anti-social behavior, and fear/anxiety. Additionally, TBI injuries have shown symptoms that are closely related to Parkinson's and Alzheimer's like-symptoms. Currently, there are no specific treatments for a TBI injury. TBI occurs in two phases,

the primary injury (physical aspect of the injury) and the secondary injury which consists of cellular process activated hours, days, and months after the initial injury. Neuroinflammation arising during the secondary injury can lead to neuronal death and involves the activation of microglia. The Endocannabinoid system (ECS) consist of two major receptors CB1 and CB2, including the endocannabinoids that activate these receptors and the enzymes involved in their synthesis and degradation. Previously published in vitro data indicates that activation of CB2 receptors in microglia decreased the production of pro-inflammatory factors; thus expression of CB2 receptor in microglia may play a role in the modulation of the immune response. This research evaluated the role of microglia activation after TBI by using CB2 receptor knockout mice (Cx3-Cnr2) which would not express the characteristic neuroprotective effects on local neural circuits. The mechanism of action in which this occurs is not fully understood. We found that Cx3-Cnr2 mice show little to no difference compared to control mice when evaluating anxiety and fear behavior using a multitude of standard behavioral tests.

40. Automated motor outcomes in genetic mouse models of neurodevelopmental disorders. Michael C Pride and Jill L. Silverman. MIND Institute and Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, CA 95817. Clinically-relevant outcome measures are required to demonstrate the test utility of innovative drug designs (like gene therapy or stem cells), as well as to validate other traditional medicinal therapies that may be in the drug discovery pipeline by biotechnological and pharmaceutical companies. However, a major rate-limiting step, is that sophisticated, well-validated, tools that provide precise, translationally relevant (i.e., the same measures in animal models and human patients) outcome parameters are underdeveloped. Our studies utilized automated treadmill walking and pressure sensitive equipment to allow for the collection of a substantial number of quantitative motor parameters such as gait, coordination, stride length, stance width, and pressure of feet (~paws). These innovative quantifiable outcomes revealed 30 metrics of posture, gait and locomotion, stride length, force development, loading, symmetry, and gait variability. Each of these measures are analogous to those being collected by clinics at the MIND Institute, Baylor and UCLA for rare genetic neurodevelopmental disorders characterized by developmental delay and ataxia, such as Angelman and Dup15q Syndromes. Both of these genetic disorders have substantial characteristic motor dysfunction. We collected digital paw prints of each of the four limbs assessed by the Mouse Specifics software. Our studies revealed mutant mice had deficits in numerous parameters on the treadmill assay, as well as in the other more commonly used motor assays. Advantages for our focused study on motor phenotypes resulting from Ube3a overexpression or deletion are the a) strong correlation between motor and social communication abilities, b) motor is highly translatable between preclinical models and human studies, making associated outcome measures extremely useful in a clinical trial, and c) these motor markers could all be used as preclinical screening outcomes for therapeutic development.

41. Identifying the cell type mediating NMDAR receptor hypofunction effects on behaviours relevant to schizophrenia. Nigel Jones[1], Elysia Sokolenko[1], Matthew Hudson[1], Jess Nithianantharajah[1,2]. 1Monash University, 2Florey Neuroscience Institute. NMDA receptor (NMDAR) antagonists produce behavioural disturbances in rodents that are reminiscent of the symptoms experienced by schizophrenia patients. The purpose of this study was to explore the cellular basis for these behaviours caused by NMDAR antagonism. Specifically, we aimed to establish whether parvalbumin-positive (PV+) interneurons and/or forebrain CaMKIIα+ pyramidal cells mediated the effects of MK801 on a variety of schizophrenia-relevant behaviours. Transgenic mice lacking the NMDAR from PV+ interneurons (PV-Cre;NR1f/f) or forebrain pyramidal cells (CaMKIIα-Cre;NR1f/f), along with their wild-type littermates, were administered varying doses of MK-801 or saline at time of testing. Behavioural outcomes were: 1) accuracy and perseveration in the Trial Unique Non-matching to Location task of working memory, 2) locomotor activity and, 3) prepulse inhibition (PPI). In WT mice, MK801 significantly ($p<0.05$) disrupted all behavioural outcomes. Deletion of the NMDAR from PV+ interneurons significantly ($p<0.05$) blunted the MK-801-induced increase in locomotion; did not alter the MK-801-induced decrease in PPI; but enhanced the drug-induced impairment in working memory accuracy and increase in

perseverative behaviour ($p<0.05$). Contrastingly, deletion of NMDAR from pyramidal cells did not alter the ability of MK-801 to exert any of these effects. These findings suggest that hyperlocomotion induced by NMDAR antagonists is mediated, at least partially, by PV+ interneurons, but deficits in sensorimotor gating, working memory and cognitive flexibility induced by NMDAR antagonism are not exclusively mediated by either PV+ or CaMKIIα cells. Further, these findings also support the concept that the heterogenous symptomatology observed in schizophrenia is created by a variety of cellular deficits.

42. Neuroprotective effect of Rutin in experimental paradigms of STZ-induced diabetic neuropathy Mittal, Ruchika[1]; Kumar, Anil[1] 1Pharmacology Division, University Institute of Pharmaceutical Sciences,UGC-CAS, Panjab University, Chandigarh 160014, India. Diabetes mellitus is a serious global health problem and its prevalence is estimated to be 366 million worldwide by the year of 2025. Diabetic neuropathyaffects more than 50% of diabetic patients and is a major cause of disability. Rutin has been demonstrated in number of pharmacological activities including anti-diabetic, anti-oxidant and anti-inflammatory activities. Streptozotocin (STZ, 55 mg/kg) dissolved in 0.1 M citrate buffer (pH 4.5) was administered intraperitoneally (i.p.) to overnight fasted rats. Animals with blood glucose level more than 250g/dl are considered diabetic and are used for further studies.Naive and diabetic rats were randomly selected and divided into eight groups of six animals in each group. Rutin (100 and 200 mg/kg,i.p.) (Sigma-Aldrich, USA) and Nimesulide (5 and 10 mg/kg, i.p) (IPCA, Mumbai) was suspended in 0.25% sodium carboxy methyl cellulose. All the behavioural parameters (Measurement of body weight, Mechanical allodynia, Cold allodynia, Mechanical hyperalgesia, Thermal hyperalgesia) were performed on day 0 , 2nd , 4th, 6thand 8thweek. On last day (of 8th week), blood was collected retro-orbitally and mean nerve conduction velocity was assessed. The animals were then sacrificed sciatic nerves were isolated for further biochemical estimations (Lipid peroxidation, Nitrite estimation, Superoxide dismutase activity, reduced glutathione (GSH) estimation, and Catalase estimation). Rutin(100 and 200 mg/kg) for 8 weeks significantly protected all the behavioral alterations (loss in body weight, mechanical allodynia, cold allodynia, mechanical hyperalgesia, thermal hyperalgesia), oxidative damage (lipid peroxidation, nitrite estimation, superoxide dismutase activity, reduced glutathione (GSH) estimation, and Catalase estimation) and change in mean nerve conduction velocity induced by STZ. Further, combination of Rutin (100 and 200 mg/kg) with Nimesulide (10 mg/kg, i.p) significantly reversed all the behavioural, biochemical and changes in nerve conduction velocity as compared to their effect per se in STZ-induced diabetic neuropathy. The present study suggests the protective effect of Rutin against STZ-induces diabetic neuropathy. Study further provides a an evidence that rutin produces better effect in combination with nimesulide against STZ-induces diabetic neuropathy.

43. Sex- and hormone-dependent effects of stress on astrocyte morphology in medial prefrontal cortex: structural atrophy in males, hypertrophy in females. Bollinger, J.L., Wellman, C.L. Department of Psychological and Brain Sciences, Program in Neuroscience, and Center for the Integrative Study of Animal Behavior. Indiana University, Bloomington, IN. Astrocytes play a critical role in regulating synaptic architecture and function. Chronic stress induces atrophy of astrocytes in medial prefrontal cortex (mPFC) in males, and ablation of astrocytes is sufficient to induce depressive-like behaviors, suggesting that these cells may contribute to stress-linked cognitive and behavioral dysfunction. Chronic stress alters neuronal architecture, microglial state, and mPFC-associated behavior in a sex- and hormone-specific manner. Likewise, astrocyte morphology can differ between males and females, and is sensitive to gonadal hormones. Therefore, we examined potential hormone-dependent stress effects on astroglial morphology in mPFC. Male and female rats underwent sham surgeries, gonadectomy (GDX), or GDX with hormone replacement (males: testosterone [T], females: estradiol [E]). After a recovery period, rats received daily restraint stress (3 h/day, 10 days) or were left unhandled except for weighing. Brains were extracted 24 h after restraint, sectioned, and stained for the astrocyte marker glial fibrillary acidic protein (GFAP). Images were collected from four sections evenly spaced across the rostral-caudal extent of the prelimbic region of mPFC. For each image, GFAP+ material was assessed in layers 1, 2/3, 5, and 6 using a standardized threshold, with summed process length- and branching- per cell examined using ImageJ's skeletonize function. At baseline,

males exhibit greater GFAP+ material in mPFC compared to females. Hormone manipulation did not alter basal astroglial morphology in males. However, astroglial state appears to be sensitive to E in females: ovariectomy did not affect GFAP+ material in mPFC, whereas non-cycling, proestrus levels of E replacement induced a tendency toward increased GFAP+ material. Chronic stress reduced the area of GFAP+ material in males, but increased this in females. Hormonal removal and replacement disrupted this pattern in both sexes. These findings indicate sex differences in- and differential stress effects on- astrocyte morphology in mPFC, and further suggest that cycling gonadal hormones may contribute to sex-specific stress effects on astroglial structure and, in turn, neural function and behavior.

44. Identifying neuroprotective in vivo targets after a traumatic brain injury. Zamora, Maria F[1], Bierbower, Sonya M[1] 1William Paterson University, Wayne, NJ 07470. Traumatic head injury (TBI) is a leading cause of death and disability among all age groups, occurring from a variety of causes, including car accidents, falls and battlefield events. Among the most common consequences of a TBI are anxiety-like behavior development in months to years after injury. Currently, there are few-to-none treatments after a TBI; a gap that this project seeks to address. In neurons throughout the brain, "M-type" K+ currents, underlied by the KCNQ family of ion channels, play dominant roles in control over excitability, and are thus implicated in myriad neurological and psychiatric disorders. Recently, the use of M-channel "openers" has emerged as novel anti-convulsive and anti-nociceptive compounds, and the FDA-approved drug, retigabine (RTG), is now in the clinic. However, beyond its anti-convulsive efficacy, we have shown in rodent models that RTG is neuroprotective against cell death, deleterious inflammation and motor impairment after a stroke, and we here show such a benefit after a TBI as well. Importantly, cytotoxic and vasogenic edema, neuronal death and morphological changes are all associated with long-term effects after a TBI. Our data indicate that M-channel openers represent a novel and powerful therapy after a TBI, not solely by reducing electrical excitability, but by reducing the inflammatory and cell edema consequences of a TBI that are linked to irreversible brain damage. We are testing this hypothesis in mice with a controlled cortical impact "blunt force" TBI that best simulates trauma after vehicular accidents or falls. The effects of RTG on brain damage. Our data so far show strong effects of RTG administered within 30 min of a TBI, with a reduction in characteristic behaviors when compared to vehicle-only controls.

45. Canca1c haploinsufficiency in juvenile rats produces sex-dependent effects on social play behavior and pro-social 50-kHz ultrasonic communication in both the sender and receiver. Theresa M. Kisko[1], Moria D. Braun[1], Susanne Michels[2], Stephanie H. Witt[3], Marcella Rietschel[3], Carsten Culmsee[2], Rainer K.W. Schwarting[1], Markus Wöhr[1] 1Behavioral Neuroscience, Experimental and Biological Psychology, Faculty of Psychology, Philipps-University of Marburg, Gutenbergstr. 18, D-35032 Marburg, Germany 2Institute of Pharmacology and Clinical Pharmacy, Philipps-University of Marburg, Karl-von-Frisch-Str. 1, D-35032 Marburg, Germany 3Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Faculty of Medicine Mannheim, University of Heidelberg, J5, D-65189 Mannheim, Germany. Social play behaviour is essential for healthy development in mammals. Rats are a highly gregarious species which shortly after birth begin displaying a complex repertoire of social play behaviour and ultrasonic vocalizations (USV). USV serve as situation-dependent affective signals and fulfill important communicative functions, e.g. positive 50-kHz USV as social contact calls. Recently a novel, yet, well established risk gene known as CACNA1C has been implicated in numerous neuropsychiatric disorders, most notably affective disorders, such as major depression and bipolar disorder, but also schizophrenia and autism. The gene encodes for the pore-forming alpha1c subunit of the L-type voltage-gated calcium channel Cav1.2, mediating depolarization-dependent calcium influx into the cell. In this study, our aim was to explore the role of Cacna1c in social behavior, specifically during the critical period of early development. Using a newly developed genetic rat model, we investigated juvenile social play behavior and concomitant 50-kHz USV emission in male and female wildtype (+/+) and heterozygous (+/-) Cacna1c rats. In addition we explored 50-kHz USV in the sender by assessing behavioral responses displayed by the recipient when exposed to 50-kHz USV playback. Our results indicate that in males there are no genotype differences in social play behavior, but male Cacna1c+/- rats

displayed less 50-kHz USV emission compared to Cacna1c+/+ controls across all three play sessions. Moreover, 50-kHz USV subtypes and their structural characteristics were affected by Cacna1c deletion. In females, in contrast, evidence for prominent genotype effects was obtained, with female Cacna1c+/- rats spending more time playing and specifically pinning more than Cacna1c+/+ controls during the second and third play session. However, increased play behavior did not result in elevated 50-kHz USV rates in female Cacna1c+/- rats and during the first play session, where play levels did not differ, 50-kHz USV were reduced. Moreover, Cacna1c haploinsufficiency affected the behavioral response in recipient rats exposed to 50-kHz USV playback. Despite that Cacna1c+/+ and Cacna1c+/- rats both displayed strong social approach behavior and presumably started to search for a conspecific in response to 50-kHz USV, strong place preference for the area in proximity to 50-kHz USV was seen in Cacna1c+/+ but not Cacna1c+/- rats after the playback presentation ended, indicating that only Cacna1c+/+ rats kept searching for a conspecific. Together, our findings suggest that Cacna1c haploinsufficiency leads to behavioral changes in social and communication development with relevance to neuropsychiatric disorders, both in sender and receiver.

46. Altered emission of isolation-induced ultrasonic vocalizations in Cacna1c haploinsufficient rat pups Rukhshona Kayumova[1], Theresa M. Kisko[1], Moria D. Braun[1], Rainer K.W. Schwarting[1], Markus Wöhr[1] 1Behavioral Neuroscience, Faculty of Psychology, Philipps-University of Marburg, Gutenbergstr. 18, D-35032 Marburg, Germany. CACNA1C is a well replicated vulnerability gene for affective disorders. Furthermore, mutations in CACNA1C have been identified to cause Timothy syndrome, which features include autism spectrum disorder (ASD). The gene encodes an alpha-1 subunit of the voltage-dependent L-type gate calcium channel Cav1.2. Studies on the effects of Cacna1c deletions in genetically modified rodents on behavioral readouts with relevance to neuropsychiatric disorders are yet sparse. In particular, little is known about the effects of Cacna1c deletions on early developmental measures. Therefore, the aim of the present study was to describe the behavioral phenotype of Cacna1c haploinsufficient rat pups. To this aim, we used a newly generated Cacna1c rat model and compared Cacna1c heterozygous (+/-) pups to wildtype (+/+) littermate controls with specific emphasis on ultrasonic vocalizations (USV). Isolation-induced USV typically increase during the first week of life and decrease thereafter, giving rise to an inverted U-shaped pattern of call emission. Therefore, they were measured at postnatal days (PND) 5, 7, 9, and 11. Behavioral phenotyping further included developmental milestones, homing test, and a pup discrimination task that was utilized to test whether mothers display genotype-dependent pup preference. Results show that Cacna1c+/- rats are viable, with the expected 50/50 genotype and sex ratios being evident in Cacna1c+/+ x Cacna1c+/- breedings. At the behavioral level, the most prominent genotype effect was seen in the emission of isolation-induced USV. While Cacna1c+/+ controls displayed the expected inverted U-shaped developmental call emission pattern, with call rate peaking at PND 9, call emission was severely delayed in Cacna1c+/- pups. Genotype effects on acoustic call features and developmental milestones were mild. In the homing test, both genotypes displayed a clear preference towards home cage bedding over fresh bedding material, reflecting intact social olfactory abilities and high levels of social motivation. Finally, mothers did not display genotype-dependent pup preference. Together, these findings indicate that Cacna1c is involved in the developmental regulation of pup ultrasonic calling. The observed delay is consistent with other rodent ASD models.

47. Phosphorylation of Mitogen-Activated Protein Kinase in the Rat mPFC and Amygdala is Associated with Individual Variation in Extinction Learning. Russo, A.S.[1] & Parsons, R.G.[1]. 1 Stony Brook University, Department of Psychology. Although most individuals are exposed to a traumatic event at some point, only a portion of individuals develops posttraumatic stress disorder (PTSD), suggesting there are predisposing factors which render some individuals more susceptible to the development of PTSD than others. Determining what makes some individuals more likely to develop PTSD has the potential to lead to the development of preventative and interventional treatments for susceptible individuals. Because individuals with PTSD have been shown to have poor extinction, PTSD is thought to be representative of a poor ability to learn or recall extinction. The amygdala,

medial prefrontal cortex (mPFC), and hippocampus are structures known to be crucial for extinction learning. Furthermore, activation of the mitogen-activated protein kinase (MAPK) cascade is known to be a crucial component of the formation of long-term memories. To identify differences in activation of structures important for extinction between different extinction phenotypes, we assessed levels of phosphorylated MAPK (phospho-MAPK) in the amygdala, mPFC, and hippocampus of adult, male Sprague-Dawley rats with good and poor extinction learning, and control rats which did not undergo associative learning. Rats were exposed to a fear conditioning paradigm, and were sacrificed either after an extinction training session or an extinction recall session the following day. The amygdala, mPFC, and hippocampus were dissected and subjected to a western blotting procedure where they were probed for phospho- and total MAPK. We found that rats which had poor within-session extinction learning and rats which had poor extinction recall had significantly less phospho-MAPK activity in the mPFC compared to rats which had good within-session extinction learning and extinction recall following extinction training and extinction recall, respectively. Furthermore, we observed a trend such that rats which had poor extinction recall had less phospho-MAPK activity in the amygdala than rats which had good extinction recall following extinction recall. We did not see differences between the low and high extinction phenotypes in the amygdala following extinction training or in the hippocampus following extinction training or extinction recall. The finding that there is less activation in the mPFC of rats with poor extinction compared to rats with good extinction, and less activity in the amygdala of rats with poor extinction recall compared to rats with good extinction recall, prompts us to ask which mPFC-amygdala connections are crucial for extinction learning, and whether activity in these circuits differs between extinction phenotypes. Future work will seek to delineate the circuitry that is important for extinction learning and recall, and how that circuitry is deviant in poor extinguishers using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs).

48. Behavioral changes across novelty habituation: Contextual modulation of self-grooming after a stress event. Mijail Rojas-Carvajal[1], Katherine Villalobos[1], Jaime Fornaguera[1,2], & Juan C. Brenes[1,3] 1Neuroscience Research Center, University of Costa Rica; 2Biochemestry Department, School of Medicine, University of Costa Rica; 3Institute for Psychological Research, University of Costa Rica. Grooming is a widespread behavior in the animal kingdom primarily geared towards the care of the body surface; nonetheless, other behavioral functions have been investigated and postulated. For example, rodents display high levels of grooming in contexts of potential threat, a fact usually interpreted as a sign of stress and anxiety. Conversely, new evidence suggests that during the process of habituation to novel and threatening contexts, particular sequences of grooming would act as a behavioral feedback facilitating emotional de-arousal. To test those opposing hypotheses about grooming interpretation, we assessed how testing contexts with different gradients of familiarity would affect exploratory activity and risk-assessment behaviors, and grooming subtypes of stressed and non-stressed rats. For that purpose, different groups of male Wistar rats were tested in one of the follow conditions: (1) in an unfamiliar open-field arena, (2) in a familiar open-field arena, (3) and in a home cage. Prior to the 20-minutes testing session, half of the animals within each testing condition were stressed by receiving three foot shocks of 1 mA 5 seconds apart. If grooming indicates stress and anxiety, it should increase at the beginning of tests, with stressed rats displaying even higher levels of grooming as compared with their non-stressed counterparts. However, if grooming facilitates emotional de-arousal, it should increase as exploration and risk-assessment decrease. In such scenario, unstressed animals tested in the familiar contexts should display the greater levels of grooming, in contrast to pre-stressed animals tested in unfamiliar contexts. Evidence will be presented about how the degree of novelty and threat associated with the testing context, may modulate defensive behaviors after an acute stress. Furthermore, the detailed analysis of the kinetic changes in grooming sequences will provide new insights into the understanding of grooming and its informative value in preclinical research. We propose that the richness of grooming interpretation lies in the careful analysis of its sub-components over time. Here, we will bring new evidence that support the hypothesis that long and complex sequences of grooming would facilitate emotional de-arousal, whereas short and head-directed sequences would be more related with ongoing stress states.

49. The right fit: Finding the ideal volume and exposure time for drug delivery in zebrafish. Frick, E. E.,[1] Caramillo, E. M.,[1] Khan, K. M.,[1] & Echevarria, D. J.[1] 1University of Southern Mississippi. The zebrafish (Danio rerio) model has emerged as a promising model for the study of various neuropsychiatric disorders such as anxiety, depression, and addiction. There is a high degree of genetic conservation between zebrafish and humans (Howe et al., 2013), which extends to the conservation of neurotransmitter pathways and receptors. This makes the zebrafish model especially suited for drug discovery. However, laboratories vary in their mode of pharmacological treatments; specifically with regard to the volume of drug solution used for the treatment. Some researchers may opt to use a low volume of solution, which has been shown to introduce a confound, increasing baseline cortisol levels. Thus, the mode of drug delivery may, inadvertently affect the behavioral and physiological response to the treatment, effectively confounding results. Our protocol sought to evaluate the behavioral and physiological profiles of stress following treatment in beakers of various sizes; animals were treated in one of four beaker volumes: 100ml, 250ml, 600ml or 1000ml. As an added measure, we also evaluated the time delay effects; animals were treated in their respective beaker for a period of either 3min, 15min, 30min. With 12 unique experimental conditions, we sought to identify a standardized dosing time and beaker volume to control for cortisol due to beaker stress isolation. Our results suggest that the beaker volume and duration prior to dosing does present differing cortisol levels which may indirectly influence any subsequent experimental manipulation. Longer treatment periods in a higher volume produce less cortisol compared to shorter treatment periods in a low volume. Conditions that fostered the highest cortisol levels were identified for further behavioral testing.

50. When Behavior Drives Neurobiological Explorations: A preliminary investigation of rodent driving responses and accompanying biomarkers of stress adaptation. Fox, N., Crawford, E., Knouse, L., Vavra, D., Kent, M., & Lambert, K. Department of Psychology, University of Richmond, VA 23173. According to a recent survey, American motorists drive approximately 30 miles a day, spending 46 minutes, appx. 5% of waking hours, driving their automobiles (AAA, 2015). Transportation in automobiles is vastly different than naturally evolved modes of self-motion—as it requires minimal energy expenditure and represents a faster mode of self-motion to intended destinations. Previous research comparing varied self-motion strategies in rodents has explored effects of accelerated and altered modes of transportation on variables such as proprioceptive feedback, vestibular processes and altered hippocampus-based navigational abilities (Terrazas et al., 2005). The purpose of the current preliminary study was to explore the effects of rodent driving training, a potential form of environmental enrichment, on stress adaptation. Accordingly, two male Long-Evans rats were shaped to enter a specially-designed vehicle and grasp a metal cable to drive the car toward a food reward. Using this model, rats learned to drive the vehicle to the goal in approximately two weeks (5-6 training sessions). After “maintenance” driving sessions over the course of eight months, the two driving-trained rats (drivers), along with age-matched rats with no driving experience (non-drivers) were moved to a larger, novel habitat. During the first week of living in the new habitat, the driver rats exhibited higher DHEA/Corticosterone levels (extracted from fecal samples); specifically, the ratios were 57% higher in the driver rats at baseline and, by the third day of the new habitat exposure, 63% higher than the non- driver rats (higher ratios are viewed as healthier responses). At baseline, the body weights of non- drivers were 20% heavier than the driving rats and, following a week in the new habitat, similar weight differences between the groups were observed. These biomarkers, in addition to responses to behavioral challenges, will continue to be monitored to determine if driving training has a positive effect on emotional resilience and well-being in a similar pattern as observed in effort-based reward training models in our laboratory (Lambert et al., 2014).

51. Sex-dependent effects of two-hit stress on behavioral flexibility in rodents. Kelly M. Moench[1] and Cara L. Wellman[1]. Indiana University. 1Department of Psychological and Brain Sciences, Program in Neuroscience, and Center for the Integrative Study of Animal Behavior, Indiana University, Bloomington, IN, USA. Exposure to multiple stressful life events increases risk for many psychological disorders, including depression and anxiety.

Women are at increased risk for these and other stress-related disorders, yet the mechanisms underlying this vulnerability are currently unknown. Animal models of stress typically focus on the immediate effects of chronic stress on brain and behavior. Using this approach, a paradoxical, male-biased vulnerability to stress has emerged, especially with regards to prefrontally mediated behaviors. For instance, male, but not female, rats exhibit stress-induced deficits in prefrontally-mediated tasks such as behavioral flexibility. We showed that chronically stressed male and female rats show differential response to a novel acute stressor in the days following chronic stress. When exposed to heterotypic acute stress following a 7-day rest period after chronic stress, female rats have an exaggerated response of the periventricular nucleus of the hypothalamus, whereas male rats do not. This suggests that exposure to chronic stress modulates later stress responsivity in a sex-dependent manner. This raises the possibility of sex differences in the cognitive ramifications of two-hit stress exposure, with females showing increased vulnerability. Here, we provide preliminary data investigating this possibility. We assessed whether prior exposure to chronic stress (restraint 3h/day, 10d) influences the effect of acute stress (30 min elevated platform stress) on behavioral flexibility using an attentional set-shifting task in male and female rats. Immediately following chronic stress, males had a deficit in behavioral flexibility specific to extradimensional shifting (EDS). This deficit was ameliorated following a 7-day post-stress rest period. Further, exposure to a heterotypic acute stressor after the 7-day rest period did not impair EDS in males. In contrast, female rats showed no deficit in set-shifting following chronic stress. Interestingly, deficits in EDS emerged in chronically stressed female rats after exposure to a heterotypic acute stressor 7 days post-chronic stress. Thus, while chronic stress may not have immediate deleterious effects on behavioral flexibility in female rats, it may alter the response to future stressors in a manner that induces maladaptive neurobiological and behavioral alterations. This pattern of results highlights the need to study sex differences in the lasting effects of chronic stress on brain and behavior.

52. Changes in Myelin Structure and Fear Behavior after Blast Induced mild Traumatic Brain Injury (mTBI)**.** William Taylor[1], Mio Nonaka[1], Andrew Holmes[1]. [1] Laboratory of Behavioral and Genomic Neuroscience, National Institute on Alcohol Abuse and Alcoholism, NIH. Traumatic brain injury (TBI) can lead to various psychiatric disorders like PTSD and depression. Blast injury is a particularly common cause of mTBI in a military setting, but little is known about how this type of injury differentially impacts brain areas. Our goal was to further illuminate how areas of the brain implicated in fear memory are impacted by blast mTBI. This was done by looking at damage to myelin structures and correlating this with changes in behavior. We subjected mice to various severities of injury and investigated structural and behavioral changes at different timepoints post injury. Changes in Trace Fear Conditioning at one week after the most severe injury were evident, as was myelin damage in images taken via electron microscopy. Immunohistochemical analysis of the injured brains showed lower density of myelin markers in large brain areas, like the hippocampus, as well as sublayer specific damage. The electron microscopy and immunohistochemistry also suggest some recovery of myelin at a later timepoint after injury. The specific sub region damage and evidenced recovery suggest new avenues of therapies for blast mTBI.

Sunday, July 1

8:00-9:00 **Keynote Speaker: Pubertal maturation of male social behavior: Multi-tasking by testosterone.**

Sisk, Cheryl, Michigan State University, East Lansing, MI, USA.

Pubertal maturation of male social behavior: Multi-tasking by testosterone. Cheryl L. Sisk, Neuroscience Program, Michigan State University. Adolescent development includes maturation of social cognition, which involves the perception of social cues and selection of a context-appropriate behavioral response. Social reward and the incentive salience of social cues are necessarily revised during adolescence as the social hub switches from family to peers. Social proficiency is acquired via behavioral adaptations to social experience. Using male Syrian hamsters to study underlying neuroendocrine mechanisms, we found that adult, but not juvenile, males form a conditioned place preference (CPP) to female chemosensory stimuli, indicating that this social cue is not rewarding prior to puberty. Testosterone-treated juvenile males do form a CPP to female odors, and this CPP is prevented by the dopamine receptor antagonist haloperidol. Thus, social reward is activated during puberty by testosterone via a dopamine receptor-dependent mechanism. We next identified an example of social proficiency in adult hamsters, i.e., a decrease in misdirected mounts with repeated sexual experience. Male hamsters deprived of testosterone during adolescence do not show this behavioral adaptation, even after testosterone replacement in adulthood. Sexual experience in adulthood induces increased expression of the transcription factor DFosB in the ventral prefrontal cortex, but only when testosterone is present during adolescence. Over-expression of the transcription factor into the ventral prefrontal cortex of males deprived of testosterone during adolescence restores the ability to reduce misdirected mounts with sexual experience. Both sexual experience and over-expression of DFosB increases the density of immature spines in ventral prefrontal cortex. These studies suggest that pubertal testosterone programs experience-dependent upregulation of ΔFosB in the ventral prefrontal cortex, leading to reorganization of prefrontal dendritic spines and heightened synaptic plasticity, which may be permissive for behavioral adaptations to social experience.

9:30-11:30 **Symposium: Regulating fear memories.** Chair: Susan Sangha, Purdue University. Co-Chair: Maria Diehl, University of Puerto Rico.

Prefrontal function in fear and avoidance: From reaction to action. Maria M. Diehl[1], Christian Bravo-Rivera[1,2], Jose Rodríguez-Romaguera[1], Pablo A. Pagán-Rivera[1], Anthony Burgos-Robles[4], Jorge Iravedra-Garcia[1], Fabiola Gonzalez-Diaz[1], Gregory J. Quirk[1] 1Department of Psychiatry, University of Puerto Rico School of Medicine, San Juan, PR 00936 2Department of Neurobiology & Anatomy, University of Puerto Rico School of Medicine, San Juan, PR 00936. Much is known about the neural circuits of conditioned fear and its relevance to understanding anxiety disorders, but less is known about other anxiety-related behaviors such as active avoidance. Using a tone-signaled, platform-mediated active avoidance task, we observed that pharmacological inactivation of the prelimbic prefrontal cortex (PL) delayed the initiation of avoidance. However, optogenetic silencing of PL neurons did not delay avoidance. Consistent with this finding, inhibitory, but not excitatory, responses of rostral PL neurons to the tone were correlated with the initiation of avoidance. To oppose inhibitory responses, we photoactivated rostral PL neurons during the tone to maintain pre-tone firing rate. Photoactivation of rostral PL (but not caudal PL) neurons at 4 Hz (but not 2 Hz) delayed or prevented avoidance. These findings suggest that the initiation of active avoidance requires inhibitory neuronal responses in rostral PL, and underscores the importance of designing behavioral optogenetic studies based on neuronal firing patterns. Ongoing studies are examining whether projections of rPL to the ventral striatum or baslolateral amygdala are necessary for active avoidance using optogenetic techniques.

Chronic ethanol impairs fear extinction retrieval, intensifies fear memory generalization, and reduces Arc expression in the infralimbic cortex. Scarlata, Miranda; Lee, Serena; Kandigian, Savannah; Hiller, Abbi; Lawson, Kate; Soler, Ivan; Ng, Alex; Mousley, Alexa; Bezek, Jessica; Dishart, Julian; Mintz, Gabi; Wang, Ziwen; Bergstrom, H Vassar College, Department

of Psychological Science, Program in Neuroscience and Behavior, Poughkeepsie, NY 12604. Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) often co-occur. Drinking tends to increase following exposure to a traumatic event and has been associated with more severe trauma-related symptoms. This raises the question of whether alcohol augments the retrieval of traumatic fear memories. The purpose of this study is to determine the neurobehavioral impact of chronic alcohol (ethanol; EtOH) on the retrieval of fear conditioning and fear extinction. Male adult C57BL/6N mice underwent auditory cued fear conditioning and were then administered 2.5 g/kg EtOH (i.p.) once daily over 5 days. Following three EtOH-free days, the fear memory was reactivated using either the conditioned stimulus (CS) or a novel frequency of tone to test cued generalization. Results revealed greater freezing behavior in response to the novel tone in the EtOH group, indicating enhanced cued fear memory generalization. Next, the impact of alcohol on the expression of a cued fear extinction memory was tested by extinguishing an established fear memory then administering alcohol and testing for extinction retrieval. Results revealed an increase in the expression of the extinguished fear memory, suggesting that alcohol may weaken extinction retrieval processes. There were no effects of alcohol on the retrieval of the original CS, a CS of weaker strength, or a contextual fear memory, and the effects on generalization and extinction retrieval reversed with the passage of time. Together, these results identify a selective effect for chronic alcohol on fear memory retrieval, with extinction retrieval decrements and generalization enhancement. Next, using immunohistochemistry we visualized and measured Arc expression in the prefrontal cortex following retrieval of the novel stimulus (generalization). Results revealed a significant reduction in Arc expression in the shallow layers of the infralimbic cortex (IL) that was associated with generalization. No effects were observed in IL deep or prelimbic cortical layers. Considering a role for the IL in inhibitory control over conditioned fear expression, these data lead to a model whereby EtOH-induced hypoactivity of the IL results in fear memory overgeneralization. Chemogenetic experiments to determine a causal role for EtOH-induced IL neuroadaptation in fear memory overgeneralization and extinction retrieval are currently underway.

Identification and manipulation of fear extinction engrams in the hippocampus. Michael R. Drew[1], Anthony F. Lacagnina[1], Christine A Denny[2]. 1Center for Learning and Memory, Department of Neuroscience, University of Texas at Austin. 2Department of Psychiatry, Columbia University. Fear extinction is a form of exposure therapy in which repeated presentations of a fearful stimulus in the absence of threat gradually reduce fear. Instead of erasing the original memory, extinction appears to create a parallel memory trace that inhibits or competes with the original memory. Acquisition of extinction learning is believed to involve plasticity in amygdala and prefrontal cortex, but the mechanisms controlling retrieval of extinction are not well understood. Based on recent evidence that activity of granule cell ensembles in the dentate gyrus (DG) is necessary and sufficient for recall of contextual fear memories, we assessed the role of these cells in acquisition and recall of contextual fear extinction. We utilized ArcCreERT2 transgenic mice to indelibly tag and manipulate granule cells active during contextual fear acquisition or extinction. When fear acquisition cells were tagged, their probability of reactivation during re-exposure to the training context was reduced after extinction training. Extinction training did not, however, reduce the overall number of cells acutely activated by context re-exposure, suggesting that extinction activates an ensemble that is distinct from the fear acquisition ensemble. To test the hypothesis that the acquisition and extinction activate unique ensembles, we used the ArcCreERT2 system to express halorhodopsin in neurons active during either fear acquisition or extinction. Silencing extinction cells in the DG increased fear during a test of extinction retrieval but had no effect during a spontaneous recovery test one month after extinction. Conversely, silencing fear acquisition cells in the DG had no effect during a test of extinction retrieval but reduced fear during the spontaneous recovery test one month later. The behavioral effects of silencing either population were specific to the conditioned context, suggesting that the manipulations modulate expression of specific contextual memories rather than general emotional states. Finally, we found that artificially activating extinction cells using ChR2 suppressed freezing during spontaneous recovery, suggesting that recovery of fear may reflect reduced activity of DG extinction neurons. Our findings suggest that contextual fear acquisition and extinction memories are coded by unique neural ensembles in the DG. Activity of fear acquisition cells is required for expression of spontaneous recovery, whereas activity of extinction cells is required for expression of fear extinction. We hypothesize that expression of fear versus extinction memories is determined by competition between ensembles in the hippocampus.

Suppressing conditioned fear in the presence of a safety cue. Sangha, Susan, Purdue University. Clinical disorders arising from maladaptive emotion regulation present a large burden on society worldwide. Many of these disorders show comorbidity, for example, addiction with anxiety disorders. Cues predicting something aversive elicit avoidance and fear behaviors whereas cues predicting reward elicit approach and reward-seeking behaviors. Cues signifying safety have the power to modulate fear and reward-seeking behaviors by informing the organism whether or not the environment is safe. Thus, safety, fear and reward behaviors, and the circuitries governing these behaviors, are intertwined. The majority of studies on reward and fear processing have been conducted in parallel, investigating the circuitries separately in primarily male subjects. If we hope to understand and treat comorbid disorders resulting from maladaptive emotion regulation increased efforts in investigating how these circuitries integrate their functions to influence behavior is needed in both male and female subjects. We have established in male rats that the amygdalocortical circuit contributes to safety-fear-reward cue discrimination. And, our results comparing males and females show that female rats do not suppress conditioned fear in the presence of the safety cue, indicating a failure to regulate fear in ¿safe¿ conditions, and they are more reward responsive during the reward cue compared to males. Since women are more than twice as likely as men to develop emotion dysregulation disorders, this paradigm offers a great opportunity to tease apart the sex differences in neural circuitry that are generating the behavioral sex differences.

9:30-11:30 **Symposium: Convergent mechanisms underlying rapid antidepressant behavioral actions.** Chair: Panos Zanos, University of Maryland, School of Medicine. Co-Chair: Todd D. Gould, University of Maryland, School of Medicine.

GLO1 inhibitors alter GABAergic signaling and exhibit fast-onset antidepressant properties. KMJ McMurray [1,2], MJ Ramaker[3], AM Barkley-Levenson[4], PS Sidhu[5], PK Elkin[6], MK Reddy[5], ML Guthrie[5], JM Cook[5], VH Rawal[6], LA Arnold[6], AA Palmer [2,3,4,7] and SC Dulawa [1,3,4] 1Committee on Neurobiology, University of Chicago, Chicago, IL, US; 2Department of Human Genetics, University of Chicago, Chicago, IL, USA; 3Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA; 4Department of Psychiatry, University of California San Diego, La Jolla, CA, USA; 5Department of Chemistry and Biochemistry, Milwaukee Institute for Drug Discovery, University of Wisconsin—Milwaukee, Milwaukee, WI, USA; 6Department of Chemistry, University of Chicago, Chicago, IL, USA; 7Department of Human Genetics, University of Chicago, Chicago, IL, USA. Current pharmacotherapies for depression exhibit slow onset, side effects, and limited efficacy. Thus, identification of novel fast-onset antidepressants represents a major unmet need. Glyoxylase 1 (GLO1) is a ubiquitous cellular enzyme responsible for the detoxification of the glycolytic by product methylglyoxal (MG). We previously reported that MG is a competitive partial agonist at GABA-A receptors. We examined the effects of genetic and pharmacological inhibition of GLO1 in two antidepressant assay models: the tail suspension test (TST) and the forced swim test (FST). Then, we examined the effects of short-term treatment with GLO1 inhibitors in three well validated models of antidepressant onset: the chronic FST (cFST), chronic mild stress (CMS) paradigm and olfactory bulbectomy (OBX) paradigm. Finally, we determined the effects of short-term GLO1 inhibitor treatment on cyclic-AMP response-binding protein (CREB) activation and brain-derived neurotrophic factor (BDNF) induction in the medial prefrontal cortex (mPFC) and hippocampus. Genetic knockdown of GLO1 or pharmacological inhibition using two structurally distinct GLO1 inhibitors (S-bromobenzylglutathione cyclopentyl diester (pBBG) or methyl-gerfelin (MeGFN)) reduced immobility in the TST and acute FST. Both GLO1 inhibitors also reduced immobility in the cFST after 5 days of treatment. Furthermore, 5 days of treatment with either GLO1 inhibitor blocked the depression-like effects induced by CMS on the FST and coat state, and attenuated OBX-induced locomotor hyperactivity. Finally, 5 days of treatment with pBBG induced BDNF and phosphorylated CREB in the hippocampus and mPFC. Conversely, 5 days of fluoxetine treatment did not produce these behavioral or molecular effects. Our findings indicate that GLO1 inhibitors may provide a novel and fast-acting GABAergic pharmacotherapy for depression.

Positive modulation of the NMDA receptor produces rapid and sustained antidepressant effect: Characterization of Rapastinel's novel mechanism of action. Pradeep Banerjee[1], Yong-Xin Li[1], John Donello[1], Jeffery Burgdorf[2], Patric K.

Stanton[3], Joseph Moskal[2] 1. Allergan Inc, USA 2. Aptinyx Inc, USA 3. New York Medical College, USA. Negative modulation of N-methyl-D-aspartate receptors (NMDARs) by compounds like ketamine (a non-competitive NMDAR open channel blocker) can produce rapid and sustained antidepressant effects. However, ketamine induces dissociation and psychotomimetic side effects which may limit its clinical use. Rapastinel (GLYX-13) also produces rapid antidepressant activity but it does so by positive modulation of NMDARs. Earlier studies have suggested rapastinel to be an NMDAR glycine site functional partial agonist. However, our recent data indicate that rapastinel exhibits a unique NMDAR pharmacology that is independent of glycine co-agonist site. Rapastinel modulates NMDAR in a concentration-dependent manner, acting as a modest glutamate co-agonist at low concentrations and as a weak partial non-competitive antagonist at relatively higher concentrations. Rapastinel's antidepressant effect is evident at low doses, and the corresponding brain concentrations of rapastinel increase NMDAR function e.g. excitatory postsynaptic currents (EPSCs) and the magnitude of long-term potentiation (LTP) in medial prefrontal cortex (mPFC). Rapastinel acts postsynaptically, as it has no effect on mPFC pyramidal cell miniature EPSCs, paired-pulse responses, or extracellular glutamate efflux. In summary, positive NMDAR modulation by rapastinel enhances NMDAR-dependent synaptic plasticity, and represents a novel pharmacological approach for producing rapid and sustained antidepressant effect.

GABA interneurons mediate the rapid antidepressant-like effects of scopolamine. Eric S. Wohleb1,2, Min Wu1, Danielle Gerhard1, Seth Taylor1, Marina Picciotto1, Meenakshi Alreja1, Ronald Duman1, 1Yale University School of Medicine, 2University of Cincinnati College of Medicine. Major depressive disorder (MDD) is a recurring psychiatric illness that causes substantial health and socioeconomic burdens. Clinical reports show that scopolamine, a nonselective muscarinic acetylcholine receptor antagonist, produces rapid antidepressant effects in individuals with MDD. Preclinical models suggest that these rapid antidepressant effects can be recapitulated with blockade of M1-type muscarinic acetylcholine receptors (M1-AChR); however, the cellular mechanisms underlying activity-dependent synaptic and behavioral responses to scopolamine have not been determined. In the current studies we provide initial evidence that the antidepressant-like effects of scopolamine are mediated by GABA interneurons in the medial prefrontal cortex (mPFC). Confocal imaging showed that both GABAergic (GAD67+) interneurons and glutamatergic (CaMKII+) neurons in the medial PFC express M1-AChR. To determine the role of M1-AChR in specific neuron subtypes we used Cre-dependent short-hairpin RNA knockdown of M1-AChR in the medial PFC. In mice, viral-mediated knockdown of M1-AChR specifically in GABAergic neurons, but not glutamatergic neurons, in the medial PFC attenuated the antidepressant-like effects of scopolamine. Immunohistology and electrophysiology showed that somatostatin (SST) interneurons in the medial PFC express M1-AChR at higher levels than parvalbumin interneurons. Indeed M1-AChR knockdown in SST interneurons in the medial PFC prevented increased neuronal activity and antidepressant-like behavioral responses following scopolamine. These studies demonstrate that scopolamine exerts antidepressant-like responses via M1-AChR expressed on SST interneurons. These results support the hypothesis that scopolamine drives activity-dependent synaptic growth and subsequent behavioral responses by an indirect, disinhibition cellular mechanism. Further our findings suggest that modulation of SST interneurons in the medial PFC may be a promising pharmacological target for developing rapid-acting antidepressant therapies.

Ketamine and hydroxynorketamines: NMDAR inhibition independent mechanisms underlying rapid acting antidepressant efficacy. Panos Zanos[1], Todd Gould[1,2,3] Departments of 1 Psychiatry, 2 Pharmacology, and 3 Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD, USA. Current approved pharmacological treatments for depression, which rely upon monoamine modulation, have a delayed therapeutic onset of several weeks to even months. In contrast, ketamine alleviates depressive symptoms within hours following a single infusion. However, clinical use of ketamine for the treatment is limited due to its side effects, including dissociation and abuse liability. While ketamine had been thought to exert its antidepressant behavioral actions primarily via inhibiting the NMDA receptor (NMDAR), other drugs that inhibit this receptor are not antidepressants in humans. We hypothesized that ketamine's unique antidepressant effects might be mediated by its metabolites. Using mice, we examined the role of NMDAR inhibition and the involvement of the hydroxynorketamine (HNK) metabolites in ketamine's antidepressant actions. In addition, we performed in vitro field excitatory post-synaptic potential (fEPSP) measurements and western blots for AMPA receptor

subunits. Side effects of ketamine's metabolites were also assessed. Our data demonstrate that NMDAR inhibition is not primarily responsible for the unique antidepressant actions of ketamine since MK-801 (another NMDAR channel blocker) does not exert the sustained effects of ketamine and the (R)-ketamine enantiomer (~4-fold lower affinity/potency to inhibit the NMDAR), exerts superior antidepressant behavioral responses compared to (S)-ketamine. We demonstrated that production of the (2S,6S;2R,6R)-HNK metabolite is critical for ketamine's long-lasting antidepressant actions. The (2R,6R)-HNK metabolite shows behavioral, electrophysiological (synaptic potentiatio) and cellular (upregulation of the GluA1 and GluA2 AMPA receptor subunits) actions, which can explain ketamine's antidepressant actions. We also demonstrated that AMPA receptor activation is necessary for (2R,6R)-HNK's effects since administration of the AMPA receptor antagonist NBQX before and after drug administration prevented its antidepressant effects in vivo. (2R,6R)-HNK does not exert ketamine-associated abuse potential or sensory dissociation side effects. We have further demonstrated robust differences in NMDAR-mediated functional outcomes between ketamine and (2R,6R)-HNK both in hippocampal slices and in vivo. Our results indicate a novel mechanism mediating ketamine's antidepressant effects, which is independent of the NMDAR inhibition, but requires AMPAR activity. Considering the lack of side effects, these findings have relevance for the development of next generation, rapid-acting antidepressants.

Faster and better: The antidepressant actions of negative allosteric modulators of GABA-A receptors. Scott M. Thompson, Departments of Physiology and Psychiatry, University of Maryland School of Medicine. Most patients with depression are treated with selective-serotonin reuptake inhibitors (SSRIs), such as Prozac. These drugs are effective in only half of patients treated and require 6-8 weeks to exert their therapeutic actions. Faster, better treatments are needed. The discovery that ketamine exerts a fast antidepressant action has galvanized the search for novel compounds that share its rapid action, but lack the side effects that prevent its widespread use. Based on our observations that preclinical models of depression-like behavioral abnormalities, such as anhedonia, are accompanied by decreases in excitatory synaptic strength at key nodes within the reward circuitry, and that SSRIs and ketamine act to restore synaptic strength in these models in parallel with their ability to restore normal reward behavior, we postulated that weakening of inhibitory synaptic strength with a negative allosteric modulator of GABA-A receptors (GABA-NAM) would exert ketamine-like fast antidepressant-like actions. Furthermore, because of their very limited expression in the brain, we hypothesized that GABA-NAMs targeting receptors containing alpha5 subunits would exert fewer side effects than ketamine, which targets NMDA receptors throughout the brain. Indeed, we have observed that a single administration of an alpha5-subunit selective GABA-NAM, such as MRK-016 or L-655,708, reverses the anhedonia induced by any one of several chronic stress protocols, including restoration of rewarding responses to sucrose, female urine, social interaction, and sexual behavior, and that these beneficial responses persist for several days. Simultaneously, alpha5 selective GABA-NAMs restore the strength of stress-weakened excitatory synapses in a rapid and persistent manner. Unlike ketamine, GABA-NAMs had no effect on rotarod performance, did not reduce prepulse inhibition (PPI), and did not elicit a conditioned-place preference or change in locomotion. Alpha5-selective GABA-NAMs thus demonstrate promise as clinically useful fast-acting antidepressants with few side effects.

9:30-10:30 **Symposium: Social environmental and genetic factors contributing to increased vulnerability to drug addiction.** Chair: Giovanni Biggio, University of Cagliari, Italy. Co-Chair: Enrico Sanna, University of Cagliari, Italy.

Transcriptional consequences of compulsive methamphetamine taking in the presence of punishment. Jean Lud Cadet, M.D. Molecular Neuropsychiatry Research Branch, NIDA Intramural Research Program, Baltimore, MD 21224. Methamphetamine (METH) addiction is mimicked in rats that self-administer the drug. However, self-administration (SA) models do not always include adverse consequences that are necessary to reach a diagnosis of addiction in humans. In the present study, we measured genome-wide transcriptional consequences of methamphetamine SA and footshocks in rat brain. We trained rats to self-administer methamphetamine for 2 weeks followed by mild footshocks for 5 days. Contingent mild shock-induced punishment reduced methamphetamine taking

in some rats (shock-sensitive, SS) but not in others (shock-resistant, SR). Afterwards, all METH rats underwent extinction tests at one day and 30 days after the last drug session. We collected nucleus accumbens (NAc) and dorsal striatum to measure gene expression with microarrays 24 hours after the second extinction test. The shock -resistant rats showed higher levels of METH seeking than the shock-sensitive rats at the second extinction test. In addition, we found that some genes were upregulated in the nucleus accumbens and dorsal striatum of the shock-resistant group. Among the upregulated genes was oxytocin in the NAc and CART in the striatum of SR rats. These observations support a regional role of neuropeptides in the brain after a long withdrawal interval when shock-resistant and shock-sensitive animals show differential degrees of incubation of methamphetamine seeking.

Reduced amygdalar endocannabinoid signalling contributes to high stress vulnerability, anxiety and excessive alcohol drinking in genetically selected alcohol preferring. Roberto Ciccocioppo[1], Marisa Roberto[2], Alessio Masi[1], Massimo Ubaldi[1], Nazzareno Cannella[1]. 1University of Camerino, School of Pharmacy, Pharmacology Unit, Camerino, Italy. 2Department of Neuroscience, The Scripps Research Institute, La Jolla, CA, USA. Addiction is a chronic multifactorial disease characterized by urge to use the drug and loss of control over its consumption. Exposure to psychoactive agents is a necessary precondition. However, genetic and social environmental factors can play a determinant role in shaping the transition from recreational drug use to excessive consumption and addiction. Data demonstrate that Marchigian Sardinian (msP) rats, an animal line genetically selected for excessive alcohol drinking, shows innate traits resembling post traumatic stress disorder (PTSD) in humans. This state is exacerbated by negative environmental conditions and is reversed by voluntary alcohol drinking or by enhanced endocannabinoid transmission. Compared to Wistar controls, msP rats have higher Fatty Acid Amide Hydrolase (FAAH) activity and reduced dialysate N-arachidonoylethanolamine (AEA) levels in the amygdala. At behavioural levels msP rats shows higher level of freezing in the fear conditioning paradigm, reflecting more pronounced anxiety in response to a negative stimulus. Freezing response is attenuated by administration of the selective FAAH inhibitor URB597 and by voluntary alcohol drinking. Furthermore, msP rats have reduced ability to extinguish negative memories associated with footshock. This behaviour is reversed by administration of URB597 or by voluntary alcohol drinking. Considering that low levels of endocannabinoid transmission is linked to excessive stress response and expression of PTSD traits it is tempting to hypothesize that msP rats drink excessive amounts of alcohol to normalize their amygdalar endocannabinoid transmission with the attempt to attenuate negative states resembling PTSD.

1:30-3:30 **Symposium: Abnormal cortical asymmetry as a target for neuromodulation in neuropsychiatric disorders.** Chair: Randy Beck, Institute of Functional Neuroscience, Perth, Australia. Co-Chair: Rohit Shankar, University of Exeter Medical School, Exeter, United Kingdom.

Historical Developmental Models and Identification of Cortical Asymmetries. Randy Beck [(1)], Jonathan Laugharne [(2)], Richard Laugharne [(3)], Wessel Woldman [(4)] Brendan McLean [(5)], Chiara Mastropasqua [(6)] Ricardo Jorge [(7)] Michael Beck [(8)] Rohit Shankar [(9)]. 1. Director, Institute of Functional Neuroscience, Perth, Australia. 2. Assoc Professor of Psychiatry, School of Psychiatry and Clinical Neurosciences, University of Western Australia. 3. Research Fellow, School of Maths, Exeter University 4. Consultant Psychiatrist, Cornwall Partnership NHS Foundation Trust and University of Exeter Medical School. 5. Lead Consultant Neurologist Royal Cornwall Hospital Trust Cornwall. 6. Research Fellow, Institute of Functional Neuroscience, Sydney, Australia. 7. Clinical Supervisor, Institute of Functional Neuroscience, Perth, Australia. 8. Research Fellow and Clinical Supervisor, Institute of Functional Neuroscience, London, Canada. .9. Consultant in Adult Developmental Neuropsychiatry – CFT Hon. Associate Clinical Professor, Exeter Medical School. Considerable evidence exists to suggest that a variety if not all cortical systems can undergo some type of plastic reorganization. Modulation of afferent input (sensory deprivation or sensory increase) to the cortical areas represents at least one factor that determines the type of reorganization observed. This innate plastic response is probably determined to a certain extent by the central integrative state of the neurons and glial components of the functional projection networks involved. The central integrative state (CIS) of a neuron is the total integrated input received by the neuron at any given moment and

the probability that the neuron will produce an action potential based on the state of polarization and the firing requirements of the neuron to produce an action potential at one or more of its axons. In some instances neuro-plastic responses and the resultant changes in activity lead to asymmetric functional levels in cortical projection networks. At some point of asymmetrical dysfunction a critical level of imbalance of activity or arousal levels between one cortical hemisphere and the other can result in a functional disconnect syndrome. This presentation explores and develops the processes of development of neuro-plastic induced cortical asymmetry.

Modulating Cortical Asymmetry: the transdiagnostic reduction of depressive and anxiety symptoms utilising a novel therapeutic approach. Randy Beck [(1)], Jonathan Laugharne [(2)], Richard Laugharne [(3)], Wessel Woldman [(4)] Brendan McLean [(5)], Chiara Mastropasqua [(6)] Ricardo Jorge [(7)] Michael Beck [(8)] Rohit Shankar [(9)]. 1. Director, Institute of Functional Neuroscience, Perth, Australia. 2. Assoc Professor of Psychiatry, School of Psychiatry and Clinical Neurosciences, University of Western Australia. 3. Research Fellow, School of Maths, Exeter University 4. Consultant Psychiatrist, Cornwall Partnership NHS Foundation Trust and University of Exeter Medical School. 5. Lead Consultant Neurologist Royal Cornwall Hospital Trust Cornwall. 6. Research Fellow, Institute of Functional Neuroscience, Sydney, Australia. 7. Clinical Supervisor, Institute of Functional Neuroscience, Perth, Australia. 8. Research Fellow and Clinical Supervisor, Institute of Functional Neuroscience, London, Canada. .9. Consultant in Adult Developmental Neuropsychiatry – CFT Hon. Associate Clinical Professor, Exeter Medical School. A major theme emerging from recent studies is that structural and functional changes in activity levels in a variety of brain regions may be used as biomarkers to indicate levels of severity and location of dysfunction in psychiatric disorders. Asymmetry of function between the right and left dorsal lateral prefrontal cortex (DLPFC) have been identified in major depressive disorder. Our group has postulated that stimulation of the proprioceptive system components can reliably produce neuroplastic remodeling or correction of asymmetry of these circuits when applied in the appropriate manner. Method: We utilized EEG imaging to identify and target asymmetrical cortical areas and exposed these areas to a variety of peripheral stimulation techniques. Results: Participants demonstrated significant changes across all categories in the Depression and Anxiety Scale (DASS) stress (p=0.05), depression (p=0.02) and anxiety (p=0.01) and on the World Health Quality of Life Checklist with a 30% improvement in overall health reported (p=0.02). Conclusions 1. Our results indicate that specific peripheral stimulation can modulate cortical asymmetry across a variety of frequency ranges and that this modulation is associated with a significant change in symptom presentation as measured by psychometric self-reporting tools. 2. We suggest that the asymmetry ratio that we have used in this study may be a more reliable metric of asymmetry that describes not only the location of the asymmetry but also the relative strength or size of the asymmetry which is a useful metric in clinical treatment. 3. A critical factor in symptom generation may be the relative difference in EEG power between frontal regions representing the total magnitude of the asymmetry and that a critical threshold level of activity both maximum and minimum in value may trigger a reversal of function in these frontal regions. This critical level of function may be related to neurotransmitter and metabolic capacity.

Clinical approaches to Treatment of Autistic Spectrum Disorders with Non-Invasive Brain Stimulation Modalities. Randy Beck [(1)], Jonathan Laugharne [(2)], Richard Laugharne [(3)], Wessel Woldman [(4)] Brendan McLean [(5)], Chiara Mastropasqua [(6)] Ricardo Jorge [(7)] Michael Beck [(8)] Rohit Shankar [(9)]. 1. Director, Institute of Functional Neuroscience, Perth, Australia. 2. Assoc Professor of Psychiatry, School of Psychiatry and Clinical Neurosciences, University of Western Australia. 3. Research Fellow, School of Maths, Exeter University 4. Consultant Psychiatrist, Cornwall Partnership NHS Foundation Trust and University of Exeter Medical School. 5. Lead Consultant Neurologist Royal Cornwall Hospital Trust Cornwall. 6. Research Fellow, Institute of Functional Neuroscience, Sydney, Australia. 7. Clinical Supervisor, Institute of Functional Neuroscience, Perth, Australia. 8. Research Fellow and Clinical Supervisor, Institute of Functional Neuroscience, London, Canada. .9. Consultant in Adult Developmental Neuropsychiatry – CFT Hon. Associate Clinical Professor, Exeter Medical School. Recent advances in knowledge relating to the organisation of neural circuitry in the human brain have increased understanding of disorders involving brain circuit asymmetry. These asymmetries, which can be measured and identified, utilizing EEG and LORETA analysis techniques, may be a factor in mental disorders. New treatments involving non-invasive brain stimulation (NIBS), including trans-cranial magnetic stimulation, direct current stimulation and vagal nerve

stimulation, have emerged in recent years. We propose that EEG identification of circuit asymmetry geometries can direct non-invasive brain stimulation more specifically for treatments of mental disorders. We will present results and describe new NIBS therapies that have been developed and delivered, and outline and describe areas they are proving effective in certain patient groups, namely Autism spectrum disorders.

Clinical approaches to Treatment of Psychiatric and Neurological disorders with Non-Invasive Brain Stimulation Modalities. Randy Beck [(1)], Jonathan Laugharne [(2)], Richard Laugharne [(3)], Wessel Woldman [(4)] Brendan McLean [(5)], Chiara Mastropasqua [(6)] Ricardo Jorge [(7)] Michael Beck [(8)] Rohit Shankar [(9)]. 1. Director, Institute of Functional Neuroscience, Perth, Australia. 2. Assoc Professor of Psychiatry, School of Psychiatry and Clinical Neurosciences, University of Western Australia. 3. Research Fellow, School of Maths, Exeter University 4. Consultant Psychiatrist, Cornwall Partnership NHS Foundation Trust and University of Exeter Medical School. 5. Lead Consultant Neurologist Royal Cornwall Hospital Trust Cornwall. 6. Research Fellow, Institute of Functional Neuroscience, Sydney, Australia. 7. Clinical Supervisor, Institute of Functional Neuroscience, Perth, Australia. 8. Research Fellow and Clinical Supervisor, Institute of Functional Neuroscience, London, Canada. .9. Consultant in Adult Developmental Neuropsychiatry – CFT Hon. Associate Clinical Professor, Exeter Medical School. Recent advances in our knowledge relating to the organisation of neural circuitry in the human brain have increased our understanding of disorders involving brain circuit asymmetry. These asymmetries, which can be measured and identified, utilizing EEG and LORETA analysis techniques, may be a factor in mental disorders. New treatments involving non-invasive brain stimulation (NIBS), including trans-cranial magnetic stimulation, direct current stimulation and vagal nerve stimulation, have emerged in recent years. We propose that EEG identification of circuit asymmetry geometries can direct non-invasive brain stimulation more specifically for treatments of mental disorders. We describe new NIBS therapies that have been developed and delivered, and suggest that they are proving effective in certain patient groups. Clinical evidence is at an early stage, but the basic science evidence and early case studies will be presented to suggest that this may be a promising new modality for treating physical and mental disorders.

1:30-3:30 **Symposium: Associative brain mechanisms underlying adaptive and maladaptive behavior.** Chair: Donna Calu, University of Maryland School of Medicine.

Managing threat-reward conflict: Strategies of conflict-based decision making. Hector Bravo-Rivera[1], Patricia Rubio-Arzola[1], Paula Rodriguez-Aquino[3,] Albit Caban-Murillo[4] and Gregory J. Quirk[2]. Depts. of Psychiatry 2 and Anatomy & Neurobiology 1, Univ. of Puerto Rico School of Medicine, San Juan, PR 00936 2, Dept. of Biology, Univ. Of Puerto Rico, Bayamon, PR 009593, Univ. of Puerto Rico Rio Piedras, San Juan, PR 009364. The pursuit of reward and avoidance are two major behavioral motivators. Failure to balance these motivators results in maladaptive behaviors and may underlie many pathological conditions. Many studies focused on the neural substrate of avoidance, as well as reward seeking. However, little is known about the interaction between avoidance and reward-seeking circuits that result in adaptive behaviors. Previous work from our group has shown that rats learn to avoid foot-shocks by stepping onto a nearby platform when they hear a 30s tone that co-terminates with a 2s shock (Bravo-Rivera et al., 2014). In the platform-mediated avoidance task, rats continually press a lever to receive a reward pellet delivered on a variable interval schedule. Avoidance comes at a cost because the food lever cannot be reached from the platform. This cost is minimal, because food is also available during the inter-tone intervals. We modified the task to increase conflict by limiting food availability to the tone period. A light indicating food availability turned on at the same time as the tone-predicting shock. We observed three different behavioral responses to this conflicting situation. 10% (8/77) rats spent all the time on the platform and never pressed for food (avoidance-preferring subgroup). This lack of food seeking can be interpreted as the cost of excessive avoidance, and is not optimal. Finally, the remaining 18% (14/77) rats engaged in excessive food seeking showing little to no avoidance (food preferring subgroup). The increased number of footshocks received by the food-preferring group is the cost of excessive food seeking and is not optimal. In contrast, 72% (55/77) rats were able to accommodate both food seeking and avoidance behaviors, by timing the occurrence of the shock (timer subgroup). Because the shock occurs 28s into the tone-light stimulus, these rats increased their food seeking during the early portion

of the tone and avoided more as the tone progressed. Together, these findings revealed different naturally-occurring sub- groups, characterized by their contrasting behavioral response to threat-reward conflict. The approach of focusing on naturally occurring behavioral differences may provide insight into the circuits that drive decision making and their potential dysfunction in anxiety or addiction related disorders.

Amygdalar mechanisms driving individual differences in Pavlovian approach and flexibility. Helen M. Nasser[1], Yu-Wei Chen[1], Kimberly Fiscella[1], Donna J. Calu[1], 1Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD, USA. The behavior of addicted individuals is characterized by a heightened motivation for drugs and an inflexibility characterized by a persistence to seek and take drugs despite negative consequences. Sign-tracking rats that approach and engage a food-associated lever cue subsequently display heightened motivation for drug-associated cues, compared to goal-trackers. Sign-tracking rats also inflexibly respond to drug-cues despite punishment. Previous work from our lab has explored the possibility that the heightened motivation and inflexibility of sign-trackers is rooted in individual differences in Pavlovian incentive learning prior to drug-exposure. We found that while both sign- and goal-tracking rats similarly attribute appetitive incentive value to first-order Pavlovian cues, sign-trackers are unable modify behavior when outcome values change. We recently sought to determine the extent to which communication of associative information between BLA and anterior portions of insular cortex (IC) supports ongoing Pavlovian conditioned approach behaviors in sign- and goal-tracking rats, prior to manipulations of outcome value. We hypothesized that the BLA mediates goal-, but not sign-, tracking approach through interactions with the IC, a brain region involved in supporting flexible behavior. We first trained rats in Pavlovian lever autoshaping to determine their sign- or goal-tracking tendency. During alternating test sessions, we gave unilateral intracranial injections of vehicle or a cocktail of gamma-aminobutyric acid (GABA) receptor agonists, baclofen and muscimol, unilaterally into the BLA and contralaterally or ipsilaterally into the IC prior to reinforced lever autoshaping sessions. Consistent with our hypothesis we found that contralateral inactivation of BLA and IC increased the latency to approach the food cup and decreased the number of food cup contacts in goal-trackers. While contralateral inactivation of BLA and IC did not affect the total number of lever contacts in sign-trackers, this manipulation increased the latency to approach the lever. Ipsilateral inactivation of BLA and IC did not impact approach behaviors in Pavlovian lever autoshaping. These findings suggest that communication between BLA and IC maintains a representation of the initially learned appetitive association that commonly supports the initiation of Pavlovian conditioned approach behavior of both sign- and goal-trackers.

Modulating aversive prediction error in the dopamine circuit. Mihaela D. Iordanova[1] Ashraf Mahmud[1,] Marie-Pierre Cossette[1], Guillem Esber[2]. 1 Department of Psychology, Center for Studies in Behavioural Neurobiology/Groupe de Recherche en Neurobiologie Comportementale, Concordia University, Montreal, Quebec, Canada, 2 Department of Psychology, Brooklyn College of the City University of New York, Brooklyn NY, USA. Learning depends on our ability to predict the future. If our predictions are correct, i.e., there is no prediction error and no further learning is necessary. In the lab, this can be modelled using the blocking paradigm where the presence of a good predictor for an outcome prevents learning about the relationship between novel cues and the same outcome. Dopamine (DA) in the Ventral Tegmental Area (VTA) has been implicated in reward prediction error. VTA DA burst firing is seen at time of unexpected but less during expected rewards. Inducing such bursts with optogenetics at time of expected rewards supports predictive learning. It remains largely unknown whether VTA DA also modulates prediction error about aversive events. Here we use the classic blocking paradigm in the Th:cre rats line in conjunction with a cre-dependent channelrhodopisn viral vector to show that inducing a dopamine transient at time of an expected footshock decreased prediction error. Further, by stimulating nucleus accumbens terminals, we show that this effect is regulated by the VTA-nucleus accumbens pathway. Current investigations of the functional role of the VTA-NAC pathway are aimed at delving deeper into the specific mechanism that prediction error acts on, i.e., attention vs. outcome processing. These data show that VTA DA transients have an opposing effect in fear to that in reward and suggest a possible valence-specific prediction error mechanism.

Encoding of outcome information in the infralimbic cortex during habits and goal-directed actions. Jacqueline M Barker1, W Bailey Glen2, David N Linsenbardt3, Christopher C Lapish3, L Judson Chandler2 1. Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA 19102 2. Department of Neuroscience, Medical University of South Carolina, Charleston, SC 29425 3. Indiana University Purdue University Indianapolis, Department of Psychology, LD 124, 402 N. Blackford St., Indianapolis, IN 46202-3275. Impairments in the ability to flexibly regulate behavior are associated with a number of neuropsychiatric illnesses, including addiction. The infralimbic prefrontal cortex (IfL-C) has consistently been implicated as a key substrate in mediating behavioral flexibility. While much research has indicated that the IfL-C is necessary for extinction learning, a separate line of work has demonstrated that lesion or inactivation of the IfL-C prevents the expression of habitual reward seeking. To investigate the role of the IfL-C in response strategy selection, we employed a behavioral paradigm in which mice self-administered sucrose on two distinct reinforcement schedules that either promote maintenance of goal-directed actions (random ratio schedule) or the development of stimulus-response habits across training (random interval schedule). We observed that during goal-directed actions, information about action-outcome relationships is encoded in the IfL-C such that firing rates within the IfL-C are bidirectionally modulated during reward presentation or omission following a response. In contrast, this encoding is lost or attenuated during habitual reward seeking. Using an optogenetic strategy, we selectively inhibited the IfL-C for 0.5 seconds following a lever press during a test session in which the action-outcome relationship was degraded. We found that inhibition at this time point was sufficient to restore use of contingencies to guide behavior. Interestingly, while IfL-C activity was modulated during consummatory behavior, this did not differ between goal-directed and habitual reward seeking conditions suggesting that information about outcome value was not differentially encoded in the IfL-C based on response strategy. Together, these findings provide insight into the neural functions underlying the development and maintenance of habitual behavior and reveal a novel functional mechanism by which IfL-C promotes habitual reward seeking.

1:30-3:30 **Symposium: Invertebrate models of natural and drug-sensitive reward.** Chair: Moira van Staaden, Bowling Green State University. Co-Chair: Robert Huber, Bowling Green State University.

Intoxicated crayfish, addicted flies, and relapsing bees: the conserved nature of drug-sensitive reward. Robert Huber[1] & Moira van Staaden[1.] 1 JP Scott Center for Neuroscience, Mind & Behavior, Department of Biological Sciences, Bowling Green State University, Bowling Green, OH 43403. Addiction sensu lato is generally considered to be a human-specific and cognitive phenomenon. However, the results of recent work from our labs and those of others have forced us to broaden this perspective. From an evolutionary stance, addictive plant alkaloids are defensive compounds which have arisen to counter herbivory, primarily from insects. The latter are the true targets of the coevolutionary arms race, thus with respect to so-called 'human drugs of abuse', humans may be little more than collateral damage. With drug addiction essentially an invertebrate phenomenon, their nervous systems offer unique opportunities for studying the basic biological mechanisms of drug effects, for exploring how the appetitive disposition is implemented in a simpler neural system, and for examining how this is related to the rewarding action of drugs of abuse. Genetically manipulable, modularly organized, and experimentally accessible, the natural reward circuits of many invertebrates, including bees, fruit flies, crickets and crayfish, exhibit strong responses to common psychostimulants. Recent studies of invertebrate drug reward provide compelling insights into the fundamental mechanisms of addiction, validate addiction as a biological rather than a predominantly cognitive phenomenon, and support parallels with the vertebrate system. For instance, naltrexone reverses both ethanol preference and protein kinase C activation in Drosophila, suggesting alternative binding sites for naltrexone, or that insects possess a system functionally related to the vertebrate opioid system. The high relapse rate of addiction is often attributed to the perseverance of high incentive salience drug-associated memories. Work employing a proboscis extension reflex paradigm in honey bees has revealed that cocaine interferes with memory processing by directly altering DNA methylation dynamics independent of incentive salience. Finally, studies exploring Pavlovian conditioning in crickets suggest that the basic principles of functioning of aminergic systems in associative

learning (i.e. the roles of octopamine and dopamine neurons for mediating appetitive and aversive signals) are conserved among insects and mammals.

Embryonal exposure to amphetamine alters behavior and dopaminergic activity in *C. elegans* adults and progeny. Ganesh Ambigapathy[1], Sirisha R. Kudumala[2], Talus J. McCowan[1], Archana Dhasarathy[1] and Lucia Carvelli[2,3]. [1]Department of Biomedical Science - University of North Dakota, Grand Forks ND. [2] Brain Institute and [3]Wilkes Honors College - Florida Atlantic University, Jupiter, FL. Amphetamine (AMPH) is used as psychostimulant, appetite suppressant, performance enhancer and to treat Attention Deficit Hyperactive Disorder (ADHD). Despite its widespread use, the long-term consequences of this drug have been poorly investigated. Among other effects, AMPH has been shown to alter the function of proteins uniquely associated with the reward system, *i.e.* the dopamine transporter (DAT). Similarly to mammals, the nematode *Caenorhabditis elegans* (*C. elegans*) exhibits changes in behaviors when treated with AMPH, and we showed that these AMPH-induced behavioral changes are largely mediated by the *C. elegans* DAT (DAT-1). Here we investigated the behavioral and functional effects caused by chronic AMPH exposure during embryogenesis in *C. elegans* adults and progeny. We found that animals that were exposed to AMPH during embryogenesis exhibited higher values of AMPH-induced behaviors with respect to control animals. Interestingly, we found that these changes were inherited by the progeny. Because DAT-1 is one of the proteins required to generate AMPH-induced behaviors in both *C. elegans* and mammals, we tested whether embryonic exposure to AMPH alters the landscape of histone methylation associated with the promoter of the *dat-1* gene. Our ChIP experiments show that at the promoter of *dat-1* of adult animals, embryonal AMPH exposure causes significant changes of specific histone markers associated with gene silencing. Interestingly, these same changes were observed also in the F1 generation. Parallel experiments demonstrate that the ability of DAT-1 to reuptake dopamine was decreased in primary cultures of dopaminergic neurons (F1 generation) originated from animals exposed to AMPH during embryogenesis (F0 generation). Taken together, these data suggest that chronic AMPH exposure during embryogenesis reduces expression of DAT-1 in adult animals and this reduction in DAT-1 expression is transmitted to progeny. Because many of the components of the dopaminergic system as well as epigenetic mechanisms are highly conserved between *C. elegans* and mammals, these results could be critical for our understanding of how drugs of abuse initiate and promote addiction in adults and future generations. This work was supported by the NIH/NIDA R01 DA042156 to LC.

The effects of alcohol on crayfish neural circuitry and behavior depend on prior social experiences. Jens Herberholz. University of Maryland, College Park, USA. Alcohol is a powerful drug with devastating impact on health and society. Despite major research efforts and great urgency, the interactions between alcohol and nervous system function are still poorly understood. Unlike other drugs of abuse, alcohol produces a concentration-dependent biphasic behavioral response (stimulation is followed by sedation), and it interacts with a large number of different neurotransmitter systems. We recently demonstrated that crayfish are behaviorally sensitive to alcohol and progress through stages of intoxication that parallel other organisms. After initial disinhibition and hyperexcitability, the animals display increased motor incoordination followed by sedation. During the early stage of intoxication, crayfish produce sequences of rapid tail flexions ("tail-flips"), which are otherwise only seen in response to strong danger signals. We were able to link these alcohol-induced behavioral effects to neural circuitry and single neurons. Most interestingly, we showed that prior social history of the animal affected the sensitivity to alcohol on both the behavioral and neural level; socially experienced animals showed higher sensitivity to alcohol compared to socially isolated animals. Current experiments investigate the neurochemistry and neurophysiology underlying these socially-mediated responses to alcohol. We are targeting two transmitters systems, GABA and serotonin, to elucidate the cellular mechanisms that differ between socially experienced and socially naïve animals. Using combinations of agonists and antagonists for GABAergic and serotonergic receptors, both in freely behaving animals and during single cell recordings in ex vivo preparations, we are aiming to identify how the socially-induced reorganization of the nervous system gives rise to differences in alcohol sensitivity. This may lead to

a better understanding of the interplay between alcohol, social experience, and (possibly conserved) cellular-molecular mechanisms from single neurons to whole animal behavior, which is difficult to accomplish in most animal models. In the long term, the results will hopefully inform related studies in other organisms of biomedical relevance and lead to better prevention and treatment options. Supported by grant 1R03AA025213-01A1.

The effect of mammalian drugs of abuse on the drug sensitive circuitry in Crayfish. Orfanakos, Vasiliki B.[1]; Shipley, Adam T.[1]; Wormack, Leah N.[1]; Nathaniel, Thomas I.[1]; Imeh-Nathaniel, Adebobola[2]; Huber, Robert[3]. 1Department of Biomedical Sciences, University of South Carolina School of Medicine, Greenville, SC, United States, 2Department of Biology, North Greenville University, Tigerville, SC, United States, 3J.P Scott Center for Neuroscience, Mind and Behavior, Bowling Green State University, Bowling Green, OH, United States. Various models of addiction have shown evidence that addiction occurs when the brain is not able to distinguish whether specific reward circuits were triggered by natural rewards, or artificially activated by addictive drugs. In a series of studies, we determined the effects of psychostimulants (cocaine, amphetamine, and morphine) in crayfish, and characterized the resulting conditioned behaviors and molecular features associated with reward in crayfish. The results from these experiments indicate the presence of drug sensitive circuitry in crayfish that facilitate exploratory behavior and appetitive motor patterns via increased incentive salience of environmental stimuli. Moreover, a context-specific alteration of c-Fos mRNA expression was observed in the accessory lobe of crayfish during drug-induced reward. With a highly organized stereotypic behavior and a simplified neuronal system that is characterized by cellular modularity, the crayfish (Orconectes rusticus) represents an excellent model for a cross-species investigation of natural reward as an important life-sustaining process.

4:00-6:00 **Symposium: Using schedules of partial reinforcement to test uncertainty effects in a learning diathesis model of anxiety vulnerability.** Chair: Todd Allen, University of Northern Colorado. Co-Chair: Justin Handy, Syracuse VA Medical Center.

Eyeblink conditioning is enhanced in behaviorally inhibited individuals in uncertain training protocols. T. Allen[1,2,3] 1University of Northern Colorado; 2Stress and Motivated Behavior Institute; 3Central New York Research Corporation. A learning diathesis model of anxiety disorders proposes that personality temperaments alter associative learning which increases the risk for the development of anxiety disorders. Recent work has focused on behavioral inhibition (BI), a temperamental tendency to withdraw from or avoid novel social and non-social situations. In addition to avoidance, BI also includes enhanced reactivity to novelty, threat, and uncertainty. It has also been hypothesized that anxiety disorders may come about through a maladaptive response to uncertainty producing hypervigilance to aversive stimuli via the amygdala. The current work used delay eyeblink conditioning in which a conditioned stimulus (CS) tone precedes and co-terminates with an unconditional stimulus (US) corneal air puff which results in learning a conditioned response (CR) eyeblink to the tone. This form of eyeblink conditioning requires cerebellar-brainstem circuitry but is also modulated by the amygdala. Findings will be reviewed in which some aspect of uncertainty resulted in an enhancement of associative learning in BI undergraduates. BI individuals in an omission protocol (in which a CR to the tone resulted in the US air puff not occurring on that trial) exhibited greater enhanced acquisition of conditioned responses as compared to 100% CS-US paired trials. It was hypothesized that the enhanced acquisition was due to the schedule of partial reinforcement when the US is omitted on CR trials. Specific schedules of partial reinforcement in which half of the trials were either CS or US alone trials inter-mixed with CS-US paired trials produced enhanced acquisition of conditioned responses that was greater than that observed with 100% CS-US paired trials. These training protocols resulted in situations where there is some uncertainty about whether the next trial would be a CS-US paired trial or a presentation of the CS or US alone and when the next CS-US trial would occur. Partial reinforcement schedules with CS or US alone trials spaced the CS-US paired training trials across a longer inter-trial interval (ITI) than delay conditioning with 100% CS-US paired trials. Subsequent work found that extending and varying ITI produced faster acquisition of conditioned eyeblinks in BI individuals. Overall, these studies support the hypothesis that uncertainty enhances associative learning in non-clinical samples which can also be applied to clinical populations with PTSD.

Enhanced acquisition and one-week retention of the classically conditioned eyeblink response in veterans self-reporting post-traumatic stress disorder symptoms. J.D. Handy[1,2], R.J. Servatius[1,2]. 1Syracuse VA Medical Center; 2Stress and Motivated Behavior Institute. According to a learning diathesis model of anxiety, perseverative fear and avoidance in post-traumatic stress disorder (PTSD) may reflect inherent biases in associative learning. Classical conditioning of the human eyeblink response is a basic form of associative learning that can be used to examine anxiety vulnerability independent of manipulations of fear and dread. In previous work, enhanced acquisition of the classically conditioned eyeblink response was evident in combat veterans self-reporting severe PTSD symptoms. This positive learning effect was also apparent in a recent study in active duty military using a partial reinforcement schedule, suggesting that differences in acquisition may be accentuated under degraded learning conditions; that is, when there is uncertainty surrounding stimulus contingencies. In this instance a 50% partial reinforcement schedule was utilized in which paired trials (500-ms pure tone conditioned stimulus [CS] co-terminated with a 100-ms air puff unconditional stimulus [US]) were interpolated with 50% CS-alone trials. Notably, significantly greater conditioned responding in PTSD persisted through an extinction period in which the CS was presented alone. We present preliminary evidence from a follow-up study in veterans which further supports enhanced eyeblink conditioning in PTSD under partial reinforcement. In this study, acquisition was assessed during two training sessions separated by one week. Greater asymptotic performance was associated with positive endorsement of PTSD symptoms during the first training session, with evidence of significantly greater retention of learning among symptomatic veterans during a second training session held one week later. Results suggest acquisition and retention of conditioned responding are heightened in PTSD, perhaps due to uncertainty in the CS-US contingency when training under partial reinforcement. These findings support a learning

diathesis model of anxiety and suggest associative learning may be one pathway through which posttraumatic dysfunction emerges in those that are vulnerable.

Partially reinforced avoidance learning reveals differences in the expectation versus the presence of shock in Wistar-Kyoto rats. Miller Daniel P.[1,3], Servatius Richard J.[2,3]. 1Carthage College, Kenosha, WI, USA, 2Syracuse VA Medical Center, Syracuse, NY, USA, 3Central New York Research Corporation, Syracuse, NY, USA. A number of studies have demonstrated that the behaviorally inhibited Wistar-Kyoto (WKY) strain acquires signaled lever-press avoidance more rapidly and is resistant to extinguishing the avoidance response when compared to Sprague Dawley (SD) rats (e.g., Servatius et al, 2008). Recently it was demonstrated that learning in behaviorally inhibited humans was less affected by partial reinforcement during Pavlovian eye blink conditioning (Allen et al., 2014). Thus we have proposed that BI is a vulnerability associated with enhanced associative plasticity which increases the risk of developing anxiety disorder. In the present study we compared avoidance acquisition in female WKY versus female SD rats receiving either 100% paired tone-shock trails, or 50% paired trials with 50% tone only trials. Both WKY groups showed higher levels of acquisition compared to either SD group. In fact, SD rats receiving 50% paired trials adopted a strategy of waiting for the first shock pulse and making an escape rather than an avoidance. In contrast, WKY rats receiving 50% paired trials showed high levels of avoidance, even on trials that were consistently not paired with shock (e.g., the first trial of each session). Further, both WKY groups made significantly more non-reinforced lever presses during an intertrial interval safety period. Our results suggest that female WKY rats are driven by the expectation of shock, even when the shock is inconsistent. In contrast, female SD rats are driven by the presence of shock, especially when the shock is inconsistent. These different approaches in expectation of and response to intermittent aversive events could explain why we see enhanced associative learning in human populations that show increased risk for the development of anxiety and stress disorders.

Applications of the learning diathesis model of anxiety disorders. R.J. Servatius[1,2,3] 1Syracuse VA Medical Center; 2SUNY Upstate Medical University; 3Stress and Motivated Behavior Institute. A Learning Diathesis Model focuses on inherent learning biases as the critical mechanism in the genesis of anxiety disorders, such as posttraumatic stress disorder (PTSD). A central proposition is biases predate and potentiate the development of anxiety disorders such as posttraumatic stress disorder (PTSD), thereby constituting a vulnerability for anxiety. The focus serves to downplay the role of stress or trauma per se, which are highly salient but provide little predictive value in understanding etiology. Behaviorally inhibit temperament constitutes one vulnerability, as biases are evident in active duty military expressing PTSD symptoms, college undergraduates, and rats. Biases are particularly evident with partial predictability between signals and aversive events. Extensions and implications of learning diathesis will be discussed. Research supported by the SMBI.

4:00-5:30 **Oral Session 3:** Chair: Kim Gerecke, Randolph-Macon College

Clozapine blunts nicotine self-administration and reinstatement of nicotine-seeking, but increases motivation for food. Andrew R. Abela[1,3], Zhaoxia Li[1], Anh D. Lê[1,2], Paul J. Fletcher[1,3]. 1Preclinical Research and Centre for Addiction and Mental Health, Toronto, ON, Canada 2Dept. Pharmacology & Toxicology, University of Toronto, Toronto, ON, Canada 3Depts. Psychiatry & Psychology, University of Toronto, Toronto, ON, Canada. People with schizophrenia display significantly higher rates of smoking than the general population, which may be due to an interaction between nicotine and antipsychotic medication. While the conventional antipsychotic drug haloperidol sometimes increases cigarette smoking in patients with schizophrenia, there is some evidence suggesting that clozapine, an atypical antipsychotic drug, may reduce nicotine use in these patients. However, the effects of antipsychotic drugs like clozapine on aspects of nicotine self-administration and reinstatement have not been systematically examined. To address these issues, we assessed the effect of clozapine on nicotine self-administration under fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement, as well as reinstatement of nicotine-seeking following a period of abstinence. To determine the specificity of its effect on nicotine reward, we also tested the effect of clozapine on responding for food reinforcement under FR and PR schedules. We also examined the effects of haloperidol, a first-generation antipsychotic drug, under some of the same behavioral conditions as clozapine. We show that clozapine inhibits nicotine self-administration and reinstatement

of nicotine-seeking, but also increases the amount of effort rats will exert for food reward. In contrast, haloperidol at a wide range of doses attenuated responding for nicotine and food reward, suggestive of a nonspecific reduction in reinforcer efficacy. These results provide experimental support for the observation that clozapine can reduce smoking in patients with schizophrenia. The observation that clozapine increased the motivation for food reward may provide a useful avenue to shed light on the mechanisms underlying the metabolic side-effects caused by clozapine and similar medications. Taken together, these findings demonstrate the potential of preclinical models for determining why clozapine apparently reduces the motivation to consume or seek nicotine, yet increases the motivation to seek food.

Differential encoding of sensitization and cross sensitization to psychostimulants and antipsychotics in nucleus accumbens D1- and D2- receptor expressing medium spiny neurons. Davide Amato[1,2], Jasper Heinsbroek[1] and Peter W. Kalivas[1]1Department of Neurosciences, Medical University of South Carolina, SC, USA 2Department of Psychiatry and Psychotherapy, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany. Background: Nearly half of all individuals diagnosed with schizophrenia abuse addictive substances such as cocaine. Currently, the neurobiological mechanisms in patients with schizophrenia that lead to cocaine abuse are unknown. A possible explanation for the co-morbidity between schizophrenia and addiction is that the rewarding properties of cocaine reverse the diminished motivational drive caused by chronic antipsychotic regimen. Moreover, chronic antipsychotic treatment can sensitize and amplify cocaine rewarding effects and exacerbate psychoses. Methods: The rewarding properties of cocaine are attributed to the differential effects of dopamine on D1 and D2 receptor-expressing medium spiny neurons (MSNs) in the nucleus accumbens (NAc). Using in vivo Ca2+ miniature microscopic imaging, we characterize the role of D1 and D2 MSN in mono- and a cross- sensitization paradigms. D1- and D2-Cre mice were injected with a Cre dependent calcium indicator (gCaMP6f) and implanted with a gradient index (GRIN) lens above the nucleus accumbens and calcium activity was recorded using a head mounted miniature microscope. Cocaine sensitization was measured after a classic repeated cocaine regiment and antipsychotic and psychostimulant cross-sensitization was measured by a single cocaine injection after chronic pretreatment with haloperidol. Results: We found that both D1-MSN and D2-MSN populations are modulated by initial cocaine experience and further modulated during the expression of cocaine sensitization. A subpopulation of D1-MSN displayed initial activation, but reduced activity during the expression of sensitization. By contrast, the majority of D2-MSNs were suppressed by initial cocaine experience, but became active during the expression of sensitization. Furthermore, activity of D1- and D2-MSNs bidirectionally correlated with the observed behavioral responses to cocaine. Cross-sensitization following haloperidol treatment led to increased behavioral responses to psychostimulants. Current experiments are set out to investigate the neuronal responses of D1 and D2-MSN during cross sensitization between haloperidol and cocaine. Conclusion: Cocaine sensitization leads to differential neuronal responses in D1- and D2-MSN and these responses are differentially correlated with the magnitude of the sensitized behavioral response. These results reveal important new insights in the neurobiological processes in the nucleus accumbens that underlie psychostimulant sensitization and provide an important new model for studying the pharmacology of antipsychotic effects on striatal function and its potential role in increasing the susceptibility of schizophrenic patients to developing drug addiction.

High ambient temperatures increase the lethality of methylenedioxymethamphetamine and methcathinone. Yu Chen, Huyen T. Tran, Courtney J. Hefflinger, Dawn E. Muskiewicz, and F. Scott Hall. Dept. Pharmacol. & Exp. Therapeutics, Coll. Pharm. & Pharm. Sci., Univ. of Toledo, OH, USA. Background. Synthetic psychoactive cathinones (SPCs) have psychostimulant and entactogenic properties similar to methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA). SPC abuse has been associated with serious adverse events, emergency room admissions, and lethal overdoses, and it has been suggested that these risks are greater for SPCs than for METH or MDMA. At low ambient temperatures we have found that many SPCS, including methcathinone, are much less lethal that METH or MDMA and produce hypothermia. Methods. LD25, LD50, and LD75 doses of MDMA were tested for lethality at low (18-20 °C) or high (32-34 °C) ambient temperatures. Methcathinone had previously been found to have no lethal effects at doses up to 160 mg/kg IP, so this dose was assessed under both temperature conditions. During testing,

temperature was assessed every at 20 min intervals for 2 hr (and upon death), and behavioral observations made at the same intervals (e.g. hyperlocomotion, seizure, 5-HT behavioral syndrome, etc.). Blood samples were taken at death or at the conclusion of the experiment, and tissue samples taken for histological analysis. Results. Under low ambient temperature conditions MDMA produced lethality at near expected rates for the LD25, LD50 and LD75 doses, while methcathinone had limited lethality. Under high ambient temperature conditions MDMA produced 100% lethality at all doses, as did methcathinone, in all cases associated with seizure. Both MDMA and methcathinone increased plasma ammonia levels and increased liver weights. Histopathological changes were observed in the liver when liver weight increased. MDMA and methcathinone generally decreased temperature under conditions resulting in death, even under high ambient conditions, although increases were observed under some conditions. Conclusions. High ambient temperatures greatly increased lethality of MDMA, effects associated with liver damage and seizure. Although our previous studies showed that there was almost no lethality produced by methcathinone, even at a dose of 160 mg/kg IP, under high ambient temperature conditions 100% lethality was observed. These findings suggest high ambient temperatures exacerbate the toxic processes producing the lethal effects of MDMA and methcathinone, and that low temperature studies may not accurately reflect the lethal potential of SPCs.

Influences of experimental conditions and stress on the escalation of ethanol consumption in male and female mice. Dawn E. Muskiewicz[1], Nichole P. Frommann[1], Bijal R. Patel[1], Audrey C. Simon[1], Zhicheng Lin[2], F. Scott Hall[1]. 1Department of Pharmacology and Experimental Therapeutics, The University of Toledo College of Pharmacy and Pharmaceutical Sciences, Toledo, OH, USA; 2Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA, USA. Background: Escalation of ethanol intake is an important criterion for the diagnosis of alcohol dependence. To produce escalation that models alcohol dependence in humans, an examination of the conditions that produce maximum escalation of ethanol intake in mice is needed. Since the dopamine transporter (DAT) has a role in escalation of ethanol consumption and DAT is affected by chronic mild stress (CMS), the interaction of these factors was examined. Methods: Experiments 1-3 used adult male and female C57BL/6J mice. Experiment 4 used adult male and female wild-type (WT) and HET DAT KO mice (HET). Experiment 1 examined the effect of different EtOH concentrations (4%, 8%, 16% and 32% v/v) using two-bottle, 24-hr access, 2 days/wk. Experiment 2 examined different intervals of availability of 16% EtOH (1, 2, or 3 days of 24-hr access, or continuous access). Experiment 3 examined the effects of a 4 bottle preference (4%, 8% and 32% EtOH v/v; and water) with 3 days of 24-hr access/wk. Experiment 4 included 4 groups: HET control (HETC), WT control (WTC), HET + CMS, and WT + CMS. Escalation was assessed using the optimal procedure defined in Expts 1 and 2. Stressors included the following schedule each week for four weeks: damp bedding (200 ml water; 2x 9-hr and 1x15-hr), 45º cage tilt (2x 15-hr and 1x 24-hr), food deprivation (3x 9-hr), strobe lighting (300 flashes/min; 2x15-hr), and water deprivation (2x 9-hr). Results: Escalation in a 2-bottle test (Expts. 1 and 2) was dependent on concentration, interval, and sex. In Experiment 3, greater levels of consumption were observed, > 15 g/kg in males and > 20 g/kg in females, but no escalation was observed. In experiment 4, female HETC produced the greatest escalation, an effect dampened by CMS. Discussion: Both interval and concentration in a limited access procedure affected escalation of ethanol consumption over time. A 4-bottle procedure did not produce escalation of ethanol intake, but did produce very high levels of ethanol intake. The ideal conditions for escalation of ethanol intake appear to be 16% ethanol 3 days/week in C57BL/6J mice. HET DAT KO was found to affect ethanol escalation after CMS in female mice only. Further experiments are needed in order to clarify the role of DAT in stress-induced alcohol consumption and escalation.

Ethanol affects neutral sphingomyelinase-induced changes in depression/anxiety state of mice. L.S. Kalinichenko[1], L. Lacatusu[1], F. Ulrich[1], E. Gulbins[2,3], J. Kornhuber[1], C.P. Müller[1]. 1Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; 2Department of Molecular Biology, University of Duisburg-Essen, Essen, Germany; 3Department of Surgery, University of Cincinnati, Cincinnati, OH, USA. Alcoholism and major depressive disorder are two of the most widespread neuropsychiatric disorders with a comorbidity rate up to 80% [Kessler et al., 1996]. However, little is known about the potentially common molecular mechanisms underlying this relation. Our previous studies showed that sphingomyelinase pathway of ceramide synthesis plays an important role in the pathogenesis of this comorbidity. Animals with hyperexpression of ASM are characterized by innate depression-like state, which can be reduced by alcohol

self-titration. This pathway is mediated by the restoration of the sphingolipid and monoamine homeostasis in the dorsal hippocampus and nucleus accumbens of depressed mice with ASM hyperexpression, but not wild type animals [Müller et al., 2017]. Here we investigated the contribution of a sister enzyme of ASM, neutral sphingomyelinase (NSM), to the interactions between depression and alcohol dependence. Female mice with hypoexpression of NSM (het/Fro) were characterized by reduced alcohol consumption in a two-bottle free-choice drinking paradigm. This effect was not found in male het/Fro mice. Analysis of behavioral pattern of female het/Fro mice have shown reduced anxiety and depression level in naïve mice. However, self-titration with alcohol in a free-choice paradigm increased the anxiety level in these animals, but did not affect wild type animals. No genotype effects were observed in the ethanol metabolism and sedative effects of ethanol in female het/Fro mice indicating that ethanol effects are not mediated by the specific features of its metabolism in the genetically modified animals. Thus, NSM is suggested to play an important role in the mechanism determining self-controlled alcohol consumption depending on the behavioral state of an individual in female animals. These findings further confirm that sphingomyelinase pathway of ceramide synthesis contributes to the development of comorbidity between altered alcohol consumption and depression/anxiety state.

4:00-5:30 **Oral Session 4:** Chair: Farida Sohrabji, Texas A&M Health Science Center

Stromalin constrains memory acquisition by developmentally limiting synaptic vesicle pool size. A. Phan[1], C. I. Thomas[2], M. Chakraborty[1], J. A. Berry[1], N. Kamasawa[2], R. L. Davis[1]; 1The Scripps Res. Inst., Jupiter, FL; 2Max Planck Florida Inst., Jupiter, FL. Establishing proper neural circuit function during development is critically important for behavior and cognitive function. However, the molecular mechanisms underlying how specific aspects of neural circuit function are developmentally determined and maintained are unclear. Here we identify cohesin complex subunit, stromalin, as a developmental negative regulator of synaptic vesicle pool size that constrains learning and memory in adult Drosophila. stromalin was identified in a Drosophila RNAi learning and memory screen as a possible memory suppressor gene. Subsequent work has shown that Stromalin knockdown (KD) in dopaminergic neurons (DAn) increased aversive olfactory memory acquisition, and that strikingly, Stromalin KD in DAn during the 3rd instar larval stage was both necessary and sufficient to enhance memory in adult flies. To assess the mechanisms underlying this behavioral effect, we examined DAn to mushroom body neuron (MBn) communication, known to be important for the formation of olfactory aversive memory. We found Stromalin KD in DAn resulted in an increased cAMP signal generated in the mushroom body (MB) heel upon DAn stimulation; however, the DAn themselves did not have increased Ca2+ responses to the stimulation, indicating Stromalin KD in DAn specifically strengthened the functional connection between DAn and MBn. We next examined whether Stromalin KD produced neuroanatomical effects in DAn that could explain this strengthened synaptic connection. While the cohesin complex is known for its role in cell division, KD of Stromalin did not change DAn cell numbers, nor did it obviously alter their morphology. Stromalin KD did however increase levels of the presynaptic marker synaptotagmin:GFP (syt:GFP) in the DAn innervating the MB lobe. Surprisingly, we found that Stromalin KD did not affect the number or size of DAn synapses using super resolution microscopy. We then turned to electron microscopy to image synaptic vesicles in DAn of the fly brain. Remarkably, DAn with reduced Stromalin had 2-fold greater numbers of synaptic vesicles and dense core vesicles than control neurons. Therefore, Stromalin KD does not affect the neuroanatomy or neural circuitry of DAn, but specifically increases the strength of otherwise normal synaptic connections by increasing synaptic vesicle numbers at the synapse. Our data demonstrate that the role of Stromalin is to developmentally suppress memory acquisition and synaptic strength by negatively regulating synaptic vesicle biogenesis.

Study on multi-Drosophila social behavior monitoring in high-dynamic-range environment by computer vision. Ching-Hsin Chen[1], Po-Yen Hsiao[1,2], Yi-Ting Chen[3], Ann-Shyn Chiang[2,3,4], Hung-Yin Tsai[1]. 1Department of Power Mechanical Engineering, National Tsing Hua University, Hsinchu 30013, Taiwan, 2Brain Research Center, National Tsing Hua University, Hsinchu 30013, Taiwan, 3Institute of Biotechnology, National Tsing Hua University, Hsinchu 30013, Taiwan, 4Kavli Institute for Brain and Mind, University of California, San Diego, La Jolla, CA 92093-0526, USA. Tracking individual Drosophila and measuring their behaviors are fundamental steps to investigate the social behavior of Drosophila. However, the social behavior experiments in brain research are often observed by researchers, and hence a huge amount

of manpower and time are consumed. In addition, the average body length of Drosophila is only 3.5 millimeters, the size is too small for observer to make the correct judgement. The purpose of this study is to construct an innovative system in which the Drosophila behavior can be monitored automatically by using computer vision and image processing methods. In this system, eighty Drosophila are placed averagely in four areas with 50 millimeters × 50 millimeters respectively and monitored at the same time. An automatic background creation method which is robust to high-dynamic-range lighting environment is proposed. Taking the advantage of the automatic background creation method integrated with background subtraction, the effectiveness and accuracy of the current system are high enough to operate in a variety of conditions. With this method, we not only can deal with some experiments which are in poor lighting environments, but also in some non-uniform lighting situations. For example, this system can process the condition of the lighting environment in optogenetic experiment, and the light in the wavelength ranging from 585 to 595 nanometers makes the environment totally lose the blue channel information in RGB color space. With this system, many parameters which describe several kinds of important behavior of Drosophila can be obtained. For example, the duration and the times of social interaction, the head positions, the head vectors, the velocities, the accelerations, the active time and passive time, the moving trajectories, the relative distances of all Drosophila, and a processed tracking video. These parameters can help the researchers to distinguish and analyze the behavior of Drosophila. Using this system for social abnormality diseases, these data indicated that Drosophila radish mutant flies in social group exhibited hyperactive movement and interactive attention deficit similar to attention deficit hyperactivity disorder (ADHD). Thus, the system provides a novel and automated platform to identify multiple flies and extracts their continuous trajectories over long temporal recordings, typically consisting of thousands of frames. The accuracy of identification recognition is 99.8% out of 21 misjudgments in 12,000 frames, and the accuracy in head position detection is 99.2% out of 205 failed detections in 24,000 heads. The overall accuracy of this system is high enough to assist neuroscientists perform the social behavior monitoring experiment and improve the brain studies significantly.

Genetic, developmental and neural correlates of excessive grooming in a Drosophila model of Neurofibromatosis type 1. Lanikea B. King[1], Seth M. Tomchik[1]. 1Department of Neuroscience, The Scripps Research Institute, Jupiter FL. Neurofibromatosis type 1 is a common genetic disorder that results in tumor formation and predisposes individuals to a range of cognitive and behavioral symptoms, including deficits in visuospatial skills, learning, language development, sleep and increased risk for neurodevelopmental disorders such as autism spectrum disorder and attention-deficit/hyperactivity disorder. The nf1-encoded neurofibromin protein (Nf1) is highly conserved from Drosophila to humans. Flies with nf1 mutations exhibit deficits ranging from impaired learning and memory to hyperactivity and sleep deficits. These phenotypes are reminiscent of the cognitive and behavioral symptoms in humans with neurofibromatosis 1. A major question is how loss of Nf1 alters neuronal circuits, leading to changes in behavior. We recently discovered that Drosophila nf1 mutants exhibit spontaneous grooming at significantly elevated frequencies (up to 7x more that wild-type controls). This provides an opportunity to dissect the neuronal roles of Nf1 in regulating repetitive, stereotyped behavior and hyperactivity in defined neuronal circuits. In order to understand how Nf1 functions in neuronal circuits controlling grooming, we carried out several sets of experiments. First, we mapped the requirement for Nf1 across subsets of neurons with RNAi. Knocking down Nf1 in a subset of putative cholinergic neurons of the ventral nervous system generated excessive grooming, suggesting that loss of Nf1 in restricted subsets of neurons underlies the behavioral phenotype. Second, we identified a narrow developmental time window in which loss of Nf1 produces excessive grooming in adulthood, suggesting a critical developmental role of Nf1 for the production of appropriate behaviors in adulthood. Finally, genetic rescue experiments revealed that the GAP-related domain is sufficient to rescue normal grooming in a mutant background. Therefore, dysregulation of Ras signaling in nf1 mutants likely drives excessive grooming. Overall, these data provide insight into the neuronal functions of Nf1 and provide a platform to dissect the molecular genetics of Nf1 signaling across neuronal circuits.

Behavioral and neuroimmunological consequences of maternal allergic asthma. Schwartzer, Jared, Church, Jamie, Mount Holyoke College, South Hadley, MA. USA. Recent clinical studies suggest that the incidence of asthma during pregnancy may increase the risk of having a child with autism or other neurodevelopmental disorders. This is hypothesized to result

from systemic changes in the maternal immune environment brought on by elevated respiratory inflammation. Importantly, research efforts linking maternal immune activation to increased autism risk have focused on the consequences of viral or bacterial infection during pregnancy, with little available research exploring the unique roles of gestational allergies and asthma on brain and behavior development. This is significant given that allergies and asthma activate a distinct branch of the immune system that may impart unique changes in offspring behavior. We have developed a novel mouse model of maternal allergic asthma (MAA) which represents a fully-integrated immune response that activates both innate and adaptive branches of the immune system in a manner that parallels the mechanism associated with allergies and asthma in humans. Female mice exposed to repeated asthma inductions throughout pregnancy produce offspring that display social behavior deficits beginning in the juvenile period and persist into adulthood, with greater deficits observed in male versus female offspring. More recently, we have begun to probe the maternal-fetal axis to identify potential biological mechanisms driving these behavioral changes. Our preliminary findings suggest that MAA results in oxidative damage to the fetal brain and disrupts tryptophan metabolism in the placenta and developing brain by altering enzyme activity in the kynurenine pathway, altering the balance of serotonergic and glutamatergic signaling. Intriguingly, MAA-exposed offspring show greater sensitivity to allergic asthma exposure by displaying exacerbated behavioral deficits brought on by elevated neuro-immune activation. These initial findings point to a causal link between maternal asthma and changes in offspring brain, immune, and behavioral development.

A high-sucrose maternal diet has enduring effects on offspring brain and behavior in rats: A possible role for neurosteroids. Daniel J Tobiansky[1,2], George Kachkovski[1], Kim L Schmidt3, Reilly T Enos[4], Chunqi Ma[1], Ryan J Tomm[1], Jordan E Hamden[5], Cecilia Jalabert[5], Stan B Floresco[1,2], E Angela Murphy[4], Kiran K Soma[1,2,5]. 1 Department of Psychology, University of British Columbia, Vancouver, BC Canada. 2 Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada. 3 Department of Biological Sciences, Simon Fraser University, Burnaby, BC, Canada. 4 Department of Pathology, Microbiology and Immunology, School of Medicine, University of South Carolina, Columbia, SC, USA. 5 Department of Zoology, University of British Columbia, Vancouver, BC Canada. Maternal nutrition can have effects on the metabolism of the offspring into adulthood. However, the effects of maternal sugar consumption on offspring brain, steroid hormones, and behaviors are unclear. In this study, we explored whether human-relevant levels of sucrose (table sugar) consumption by rat dams had enduring effects on the offspring. In particular, we examined offspring metabolic function, neuroendocrine signaling, and motivated behaviors. Rat dams were fed either a diet containing sucrose (25% of daily kCal) or an isocaloric, matched, control diet (0% sucrose) for 10 weeks before impregnation, during gestation, and during lactation. After weaning, all offspring were placed on standard lab chow diet. From 9 weeks to 5 months, sucrose-exposed male offspring weighed less than control male offspring, and sucrose-exposed male and female offspring had a lower body mass index at 5 months. When given a choice of specialized diets [control (10% fat, 0% sucrose) vs. sucrose (10% fat, 25% sucrose) vs. high-fat (40% fat, 0% sucrose)] in a food preference test, sucrose-exposed male offspring consumed greater quantities of the sucrose and high-fat diets. Motivation to obtain a sugar reward was assessed using a progressive ratio schedule of reinforcement with sugar pellets as the reinforcer. Sucrose-exposed male (but not female) offspring displayed increased motivation to obtain sugar. Previous research suggests that diet-induced differences in motivation might be related to changes in dopamine signaling and local levels of neuroactive steroids in the mesocorticolimbic reward system (ventral tegmental area, nucleus accumbens, medial prefrontal cortex). Here, we used ultra-sensitive liquid chromatography-tandem mass spectrometry to examine circulating and hyperlocal levels of neuroactive steroids (e.g., testosterone, corticosterone, and estradiol), and qPCR to examine mRNA levels of steroidogenic enzymes, steroid receptors, and dopamine receptors. Overall, we found system-wide alterations in neurosteroid and dopamine receptor densities along with changes in steroidogenic enzyme concentrations. Thus, early-life exposure to human-relevant levels of sucrose disrupts the dopamine and neuroendocrine systems. Taken together, the results suggest that maternal sucrose consumption has enduring sex-specific effects on offspring brain and behavior, particularly with regard to choosing and obtaining highly palatable food rewards. These behavioral effects could eventually lead to metabolic disorders in the offspring if there is access to foods high in sugar and/or fat.

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