IBNS
International Behavioral Neuroscience Society

Annual Meeting Program and Abstracts

Victoria, British Columbia, Canada

June 2-7, 2015

Abstracts of the 24th Annual Meeting of the International Behavioral Neuroscience Society

Volume 24, June 2015

Contents

IBNS CENTRAL OFFICE

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PRESIDENTIAL WELCOME

Stephen Kent, PhD
IBNS President
Head of School, Associate Professor
School of Psychological Science
La Trobe University
Melbourne (Bundoora), VIC Australia
http://www.latrobe.edu.au/psy/about/staff/profile?uname=SPKent

Dear Conference Participants, Colleagues, and Friends,

It is my pleasure to welcome you to the 24th Annual Meeting of the International Behavioral Neuroscience Society in Victoria, British Columbia, Canada. I am thrilled to report that this year's meeting is on track to be our largest ever with more than 295 registrants. Examining the program one cannot help but be blown away by the quality, diversity, and international nature of the science on hand. We have world renowned keynote speakers in George Koob, Director of the National Institute on Alcohol Abuse and Alcoholism, Bill Deakin, a UK-based researcher who has been at the forefront of investigations of the role of glutamate in schizophrenia, and Jaak Panksepp, who 25 years ago coined the term 'affective neuroscience'. The rest of the scientific program is jam-packed with 23 symposia; this is more than ever before and the Program Committee had no choice but to turn down many submissions. The topics covered in these range from neurogenesis, brain lipids, drug addiction, sex hormones, autism, stress resilience, and animal models of neuropsychiatric conditions to name but a few. To cap it all off we have a symposium honouring the memory and influence of our beloved former President, Bob Blanchard, who sadly passed away in 2014. All this takes place in the Victoria Conference Centre on beautiful Vancouver Island. Make sure you find time for whale watching – I hear the orcas are always available for a photo-opportunity.

I would like to extend my thanks to the hard-working Program Committee Chaired by Mikhail Pletnikov with Jonathan Brigman as Co-Chair (Jared Young, David McKinzie, Tomasz Schneider, Cliff Summers, Dawn Eagle, Stella Vlachou, Matthew Hale, Raquel Martinez, Natalie Peartree). Until you have organised a meeting of this size you don't fully understand the work that goes in to selecting symposia, inviting speakers, etc that begins almost as soon as the last meeting ends. This committee works hand-in-glove with our Executive Coordinator Marianne Van Wagner and her assistant Alison Watson who choreograph our stimulating meetings in appealing locales.

Similar to last year, as a group we have raised over $1000 to aid a local group. This year we are providing yoga mats to the Boys and Girls Club of Greater Victoria and Vinyasa Yoga for Youth. I'd like to acknowledge the massive contribution of Matt Young in making this happen by working with Kim Gerecke and her Education & Training Committee.

As always, the core function of IBNS is to encourage research in behavioral neuroscience by fostering free and open communication and scientific exchange among its members. Our meetings are the principal avenue by which this function is realized; they succeed in doing so only due to the warm, friendly, and engaging nature of its members. I am thrilled to see each and every one of you here and look forward to our discussions.

Best wishes,

Stephen Kent
President, the International Behavioral Neuroscience Society

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TRAVEL AWARDS

We are pleased to announce the recipients of the IBNS Travel Awards for the 2015 meeting in Victoria, BC, Canada. 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 Elsevier and the IBNS members.

Postdoctoral Travel Awards

Sarah Jablonski, Cincinnati Children's Hospital Medical Center, USA

Joseph McQuail, University of Florida, USA

Jules Panksepp, Oregon Health and Science University, USA

Graduate Student Travel Awards

Franklin Back, Universidade Federal de Santa Catarina, Brazil

Jacqueline- Marie Ferland, University of British Columbia, Canada

Mouna Haidar, The Florey Inst. of Neuroscience and Mental Health, Australia

Joshua Haight, University of Michigan, USA

Daniel Hoops, The Australian National University, Australia

Christopher Fitzpatrick, University of Michigan, USA

Kanza Khan, University of Southern Mississippi, USA

Richard Matta, University of Guelph, Canada

Leah Mayo, University of Chicago, USA

Morgane Milienne-Petiot, University of California, San Diego, USA

Andrew Murtishaw, University of Nevada, Las Vegas, USA

Eric Parise, Florida State University, USA

Patrick Piantadosi, University of British Columbia, Canada

Esther Remmelink, VU University Amsterdam, Netherlands

Steven Tran, University of Toronto, Canada

Undergraduate Student Travel Awards

Jason Alipio, California State University, San Bernardino, USA

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The IBNS would like to express our gratitude to the following organizations that have given financial support to the 24th International Behavioral Neuroscience Society Conference.

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All of these companies will be onsite during the meeting. Please take time to stop by and thank them 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:

Program Committee

Mikhail Pletnikov, Chair, John Hopkins Univ. Sch. of Medicine, Baltimore, MD, USA
Jonathan Brigman, Co-Chair, University of New Mexico HSC, Albuquerque, NM, USA
Stephen Kent, La Trobe University, Melbourne, Australia
Jared W. Young, UCSD, La Jolla, CA, USA
David McKinzie, Eli Lilly & Company, Indianapolis, IN, USA
Tomasz Schneider, University of Oxford, Oxford, UK
Cliff H. Summers, University of South Dakota, Vermillion, SD, USA
Dawn Eagle, University of Cambridge, Cambridge, UK
Stella Vlachou, Dublin City University, Dublin, Ireland
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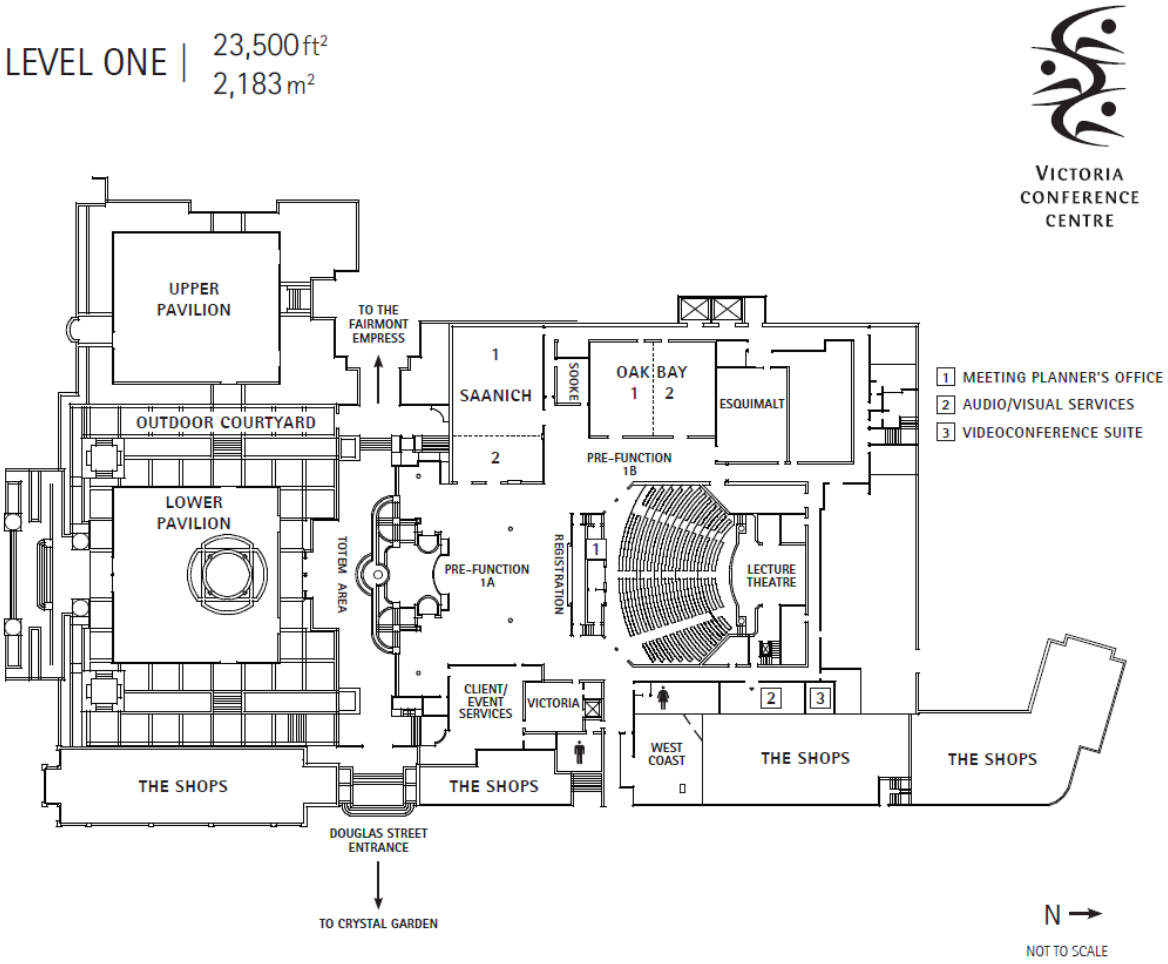
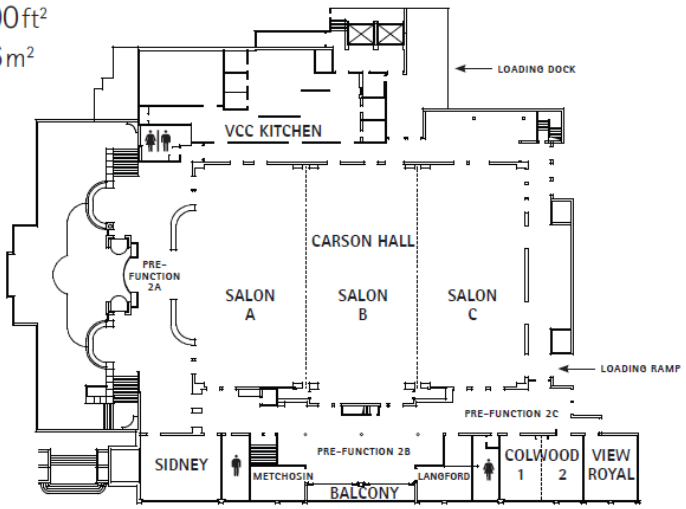
Any IBNS member who would like to become more involved in the Society may volunteer to serve on an IBNS committee. Committee details can be found on our website at http://www.ibnsconnect.org/committees

FLOOR PLAN

LEVEL ONE | 23,500 ft² 2,183 m²



LEVEL TWO | 24,500 ft² 2,276 m²



PROGRAM

REGISTRATION: The registration desk will be located outside of the Lecture Theatre on the first floor of the Victoria Conference Centre. Please plan to pick up your badge from 5:30-6:30 p.m. on Tuesday, June 2. Name badges are required for ALL events. There will be a $10 fee for replacement badges. Registration will also be open prior to the 8:00 a.m. sessions for late arrivals.

Tuesday, June 2

2:00 Council Meeting

5:00 Student & Postdoctoral Social

This event will take place in the Esquimalt Room at the Victoria Conference Center. We welcome all undergraduate student, graduate student, and postdoctoral trainees to attend. Be this your first IBNS meeting, or your tenth, the Student and Postdoctoral Social is a great way to kick off the meeting and network with trainees from around the world! In addition to refreshments and great company, you will have the opportunity to compete for a door prize by participating in a team-networking exercise.

6:30 Welcome Reception - *Courtyard of the Victoria Conference Centre*

Wednesday, June 3

8:00-10:00 **Symposium**: **Decision-making in animal models for neuropsychiatric disorders.** Chairs: **Kiyofumi Yamada, Wen-Sung Lai.** *Lecture Theatre*

8:00 From reward prediction error to dopamine hypothesis of psychosis: Insights from Akt1 mutant mice and schizophrenic patients. Lai, Wen-Sung; Chen, Ching; Liu, Hung-Hsiang; Liu, Ya-Wen; Li, Chia-Tzu; Chen, Yao-Chu; Liu, Chih-Ming; Hsu, Yung-Fong.

8:30 The insular GABAergic system controls decision-making in healthy and drug-dependent animals. Hiroyuki Mizoguchi and Kiyofumi Yamada.

9:00 Inhibitory control in young and aged rats and its gating by basal forebrain neuronal inhibition. Mayse, Jeffrey D; Nelson, Geoffrey M; Avila, Irene; Gallagher, Michela; Lin, Shih-Chieh.

9:30 The role of Orbitofrontal circuit in supporting learning driven by errors in reward prediction. Takahashi, Yuji; Schoenbaum, Geoffrey.

8:00-10:00 **Molecular mechanisms of cocaine-induced cellular and behavioral plasticity.** Chairs: **David Dietz, Mary Kay Lobo.** *Oak Bay Rooms*

8:00 Cocaine-induced transcriptional regulation of mitochondrial biogenesis in nucleus accumbens neuronal subtypes. Ramesh Chandra, T. Chase Francis, Prasad Konkalmatt, Michel Engeln, Leah Jensen, Amy M. Gancarz, Sam A. Golden, Gustavo Turecki, Scott J. Russo, David M.Dietz, and Mary Kay Lobo.

8:30 A novel role for TGF-β signaling in cocaine abuse. Gancarz-Kausch, Amy; Schroeder, Gabrielle; Humby, Monica; Mueller, Lauren; Caccamise, Aaron; Neve, Rachael; Dietz, David.

9:00 Emerging roles for neuron-astrocyte interactions in the neuropathology of cocaine abuse. Reissner, Kathryn J.

9:30 Cocaine-induced neuroplasticity: At the crossroads of addiction and psychiatry. Pletnikov, Mikhail.

10:30-11:30 **Keynote: George F. Koob**, NIAAA, NIH, Rockville, MD, USA. The neurobiology of emotions: Insights from the neurobiology of addiction. *Lecture Theatre*

1:00-3:00 **Travel Award Blitz.** Chairs: Kim Gerecke; Jill Silverman *Lecture Theatre*

1:00 Fluoxetine exposure during adolescence disrupts spatial memory performance in adulthood. Alipio[Travel Award], Jason B.; Cruz, Bryan; Shawhan, Kristi L.; Riggs, Lace M.; Iniguez, Sergio D.

1:06 Interplay between glutamatergic and cannabinoid systems within the dorsal periaqueductal gray matter modulates fear memory encoding and defensive behavior expression in an olfactory conditioning paradigm. Back[Travel Award], Franklin; Carobrez, Antonio.

1:12 Baseline poor-decision making on a rat gambling task is exacerbated following cocaine self-administration and incubation of craving: investigating individual vulnerability to addiction. Ferland[Travel Award], Jacqueline-Marie N.; Winstanley, Catharine A.

1:18 Sodium butyrate increases contextual fear expression in sign- but not goal-trackers. Fitzpatrick[Travel Award], Christopher J.; Wood, Marcelo A.; Morrow, Jonathan D.

1:24 Control of the septohippocampal pathway and learning and memory by relaxin-3/RXFP3 neural networks: Viral-based studies in transgenic mice. Haidar[Travel Award], Mouna; Hawkes, David; Guevremont, Genevieve; Olucha-Bordonau, Francisco; Ma, Sherie; Bathgate, Ross; Timofeeva, Elena; Smith, Craig; Gundlach, Andrew.

1:30 Establishing a role for cortico-thalamic circuitry in cue-driven behaviors. Haight[Travel Award], Joshua; Fraser, Kurt; Akil, Huda; Ferguson, Susan; Flagel, Shelly.

1:36 The evolution of brain structure in dragon lizards. Daniel Hoops[Travel Award], Jeremy F. P. Ullmann, Andrew L. Janke, Marta Vidal-Garcia, Timothy Stait-Gardner, Yanurita Dwihapsari, William S. Price, Martin J. Whiting, J. Scott Keogh.

1:42 Neonatal (+)-methamphetamine exposure impairs egocentric learning in the Cincinnati water maze (CWM) and working memory in the radial water maze (RWM) in rats. Jablonski[Travel Award], Sarah; Gutierrez, Arnold; Tee, Trisha; Suttling, Kathryn; Williams, Michael; Vorhees, Charles.

1:48 Assessing the effects of light dark manipulation and caffeine exposure on zebrafish sleep behavior. Khan[Travel Award], Kanza; Lodinger, Natalie; Collier, Adam; Caramillo, Erika; Echevarria, David.

1:54 The role of hippocampal dopamine D2-type receptors in the social transmission of food preferences in male and female mice. Matta[Travel Award], Richard; Underwood, Emily A.; Leach, Zoe K.; Vertes, Alex C.; Choleris, Elena.

2:00 Characterizing responses to a de novo alcohol-associated cue in healthy social drinkers. Mayo[Travel Award], Leah M; de Wit, Harriet.

2:06 Subtypes of prefrontal cortical NDMA receptors in working memory and normal aging. McQuail[Travel Award], JA; Beas, BS; Simpson, K; Setlow B; Bizon, JL.

2:12 Assessing the treatment predictive validity of model animals of bipolar mania. Milienne-Petiot[Travel Award], Morgane; Enkhuizen van, Jordy; Geyer, Mark A; Young, Jared W.

2:18 An evaluation of peripheral insulin disruption on behavior, phosphorylated tau levels, and microglia activity. Murtishaw[Travel Award], Andrew S.; Heaney, Chelcie F.; Bolton, Monica M.; Belmonte, Krystal Courtney D.; Langhardt, Michael M.; Kinney, Jefferson W.

2:24 Akt signaling within the nucleus accumbens regulates functional reactivity to chronic social defeat stress in male mice. Parise, Eric M[Travel Award]; Alcantara, Lyonna F; Sial, Omar K; Nestler, Eric J; Bolanos-Guzman, Carlos A.

2:30 Regulation of discriminative fear conditioning by prefrontal and striatal subregions. Piantadosi[Travel Award], Patrick; Yeates, Dylan; Floresco, Stan.

2:36 A novel task to assess reversal learning in mice in a home-cage environment. Remmelink[Travel Award], Esther; Verhage, Matthijs; Smit, August B.; Loos, Maarten.

2:42 Individual differences in locomotor activity correlate with behavioral responses to ethanol in zebrafish: Potential roles of the dopaminergic and serotonergic neurotransmitter systems. Tran[Travel Award], Steven; Nowicki, Magda; Muraleetharan, Arrujyan; Chatterjee, Diptendu; Gerlai, Robert.

3:30-4:30 **Neuronal correlates of rodent empathy.** Chairs: **Ksenia Meyza, Ewelina Knapska.**
Lecture Theatre

3:30 Modeling vicarious fear in adolescent mice. Panksepp, Jules.

3:45 Affective drivers for helping behavior in rats. Inbal Ben-Ami Bartal.

4:00 Neural mechanisms of fear conditioning by proxy: Social transmission of fear in rats. Monfils, Marie-H.

4:15 Neuronal circuits underlying emotional contagion. Knapska, Ewelina.

3:30-4:30 **From the lab bench to the field: Translational research approaches for investigating mild Traumatic Brain Injury (mTBI).** Chair: **Chand Taneja.**
Oak Bay Rooms

3:30 Evaluating chronic cognitive deficits in rats across a spectrum of TBI severities. Vonder Haar, Cole.

3:45 The effects of multi-trauma on mild TBI outcome. McDonald, Stuart.

4:00 Can 3D Multiple Object Tracking (MOT) be used to indicate Mild Traumatic Brain Injury? Christie, B.R., Kowalski, K., Drabkin, L., Gagnon, I.

4:15 Treatments and biomarkers for mild traumatic brain injuries. Shultz, Sandy; Wright, David; Tan, Xin; O'Brien, Terence.

4:30-5:30 **Basic and translational aspects of drug addiction.** Chair: **Jean Lud Cadet.** *Lecture Theatre*

4:30 Epigenetic and transcriptional bases of methamphetamine addiction. Jean Lud Cadet.

4:45 Basic and translational aspects of impaired dopamine signaling in methamphetamine-induced cognitive dysfunctions. Keefe, Kristen; Barker-Haliski, Melissa; Pastuzyn, Elissa; Garris, Paul; Howard, Christopher.

5:00 Molecular mechanisms underlying incubation of methamphetamine craving. Krasnova, Irina; Ladenheim, Bruce; McCoy, Michael; Shaham, Yavin; Cadet, Jean Lud.

5:15 Glutamatergic medications for substance use disorders -- are we any closer? Lucas W. Watterson, Peter R. Kufahl, and M. Foster Olive.

4:30-5:30 **Brain lipids in neuropsychiatric disorders.** Chairs: **Christian P. Müller, Miriam Schneider.** *Oak Bay Rooms*

4:30 Effects of decreased DHA in the adult brain: Implications for depression. Levant, Beth.

4:45 Omega-3 deficiency impacts dopamine related functions. Moghaddam, Bita; Lotfi, Sima; Sesack, Susan; Flores, Cecilia.

5:00 Sphingolipids: from depression and anxiety to alcoholism. Christian P. Müller, Thomas Stöckl, Eva Sprenger, Jens Tiesel, Sabine Huber, Davide Amato, Erich Gulbins, Martin Reichel, Johannes Kornhuber.

5:15 The modulatory impact of endocannabinoid signaling on adolescent drug abuse. Schneider, Miriam.

6:00-8:00 Poster Session 1 *Saanich Rooms and Pre-Function Area*

1. Age and gender relate to performance on a lexical decision task and change in negative affect in a population of daily smokers with elevated depressive symptoms. Alexandra N. Houston-Ludlam, Avery D. Mitchell, Catalina Kopetz, Reinout W.H.J. Weirs, Laura MacPherson.
2. Creatine transporter knockout mice show increased anxiety, increased depressive-like behaviors, and reductions in sociability. Kokenge, Amanda N; Skelton, Matthew R.
3. Exercise tolerance as a predictor of recovery from concussion in adolescent athletes. Hinds, Andrea; Leddy, John; Baker, John; Willer, Barry.
4. Skipping breakfast disturbs early stages of cognitive processing. An ERP study. Gonzalez-Garrido, Andres; Brofman-Epelbaum, Jacobo; Gomez-Velazquez, Fabiola; Balart-Sanchez, Sebastian.
5. Social defeat during adolescence escalates adult cocaine self-administration: Role of adolescent social experience and adaptive coping behaviors. Burke, Andrew R.; Miczek, Klaus A.
6. An evaluation of peripheral insulin disruption on behavior, phosphorylated tau levels, and microglia activity. Murtishaw, Andrew S.; Heaney, Chelcie F.; Bolton, Monica M.; Belmonte, Krystal Courtney D.; Langhardt, Michael M.; Kinney, Jefferson W.
7. Relaxin-3/RXFP3 networks in food intake and stress responses - neural mechanisms underlying behavioural effects. Blasiak, Anna; Kania, Alan; Lewandowski, Marian H.; Gundlach, Andrew L.
8. Long-term exposure to high corticosterone levels enhances glutamatergic but does not alter GABAergic transmission in the rat motor cortex. Blasiak, Anna; Kula, Joanna; Czerw, Anna; Tylko, Grzegorz; Hess, Grzegorz.
9. Muscimol applied to the dorsolateral periaqueductal gray matter impairs the negative valence instruction from a stressful experience. Carobrez, Antonio P; Giachero, Marcelo.
10. Opioid modulation of responses to social rejection in humans. Bershad, Anya K; de Wit, Harriet.

11. Major impact of the first-line antiepileptic treatment choice on the second-line treatment efficacy in a mouse model of absence epilepsy. Martin, Benoit; Kuchenbuch, Mathieu; Hadjadj, Sarah; Dieuset, Gabriel; Costet, Nathalie; Javaudin, Loic; Wendling, Fabrice; Biraben, Arnaud.
12. Conditioned object preference: a novel measure of drug-seeking in rodents. Kennedy, Bruce; Kohli, Maulika; Maertens, Jamie; Marell, Paulina; Gewirtz, Jonathan.
13. Adolescent antidepressant treatment induces an enduring anxiogenic behavioral phenotype in adulthood. Cruz, Bryan; Shawhan, Kristi L.; Rodriguez, Ricardo; Zamora, Norma; Ahmed, Raisa; Hernandez, Mirella; Motley, Lisa.
14. Reduced levels of Cacna1c modify mesolimbic dopamine system function. Terrillion, Chantelle; Dao, David; Cachope, Roger; Lobo, Mary Kay; Puche, Adam; Cheer, Joseph; Gould, Todd.
15. Genetic difference in serial reversal learning in mice. Heyser, Charles, J.
16. Influence of adversity on maternal behavior of mothers that consumed alcohol during pregnancy: Short- and long-term effects on offspring. Charlis Raineki; Parker J. Holman; Samantha Baglot; Dylan C. M. Yeates, Vivian Y. Y. Lan; Wayne Yu; Joanne Weinberg.
17. Intermittent access to palatable foods: a comparison of sugar, fat and sweet-fat food consumption in adolescent male and female rats. Tenk, Christine; Felfeli, Tina; Adrian, Allison.
18. Increased basal and stress-induced cortisol levels are associated with accelerated cellular aging in middle-aged women. Barha, Cindy; Salvante, Katrina; Hanna, Courtney; Wilson, Sam; Robinson, Wendy; Nepomnaschy, Pablo.
19. Neuropathological Changes in Concussion. Ciro Visone.
20. Relaxin-3/RXFP3 signalling promotes motivational drive and stress resilience in mice. Smith, Craig; Hosken, Ihaia; Walker, Andrew; Chua, Berenice; Zhang, Cary; Denton, Derek; McKinley, Michael; Lawrence, Andrew; Timofeeva, Elena; Gundlach, Andrew.
21. The evolution of brain structure in dragon lizards. Daniel Hoops, Jeremy F. P. Ullmann, Andrew L. Janke, Marta Vidal-Garcia, Timothy Stait-Gardner, Yanurita Dwihapsari, William S. Price, Martin J. Whiting, J. Scott Keogh.
22. Unilateral implantation of dopamine in the caudate nucleus attenuates motor abnormalities in the model hemiparkinsonism in the rat. Vázquez Matías Daniel Aarón, Valverde Aguilar María Guadalupe, Mayen Díaz Rodrigo, Sánchez Cervantes Ivonne Grisel, López Martínez Irma , Colín Barenque Laura, Velázquez Paniagua Mireya, and Vergara Aragón Patricia.
23. Acute stress in humans paradoxically enhances allocentric bias in a dual-strategy virtual Morris water maze. Mediation by sympathetic stress response? van Gerven, Dustin; Skelton, Ronald.
24. Akt signaling within the nucleus accumbens regulates functional reactivity to chronic social defeat stress in male mice. Parise, Eric M; Alcantara, Lyonna F; Sial, Omar K; Nestler, Eric J; Bolanos-Guzman, Carlos A.
25. The role of the cholinergic midbrain in sensory filtering and sensorimotor gating. Azzopardi, Erin; Schmid, Susanne.
26. The freely chosen tapping frequency of the index finger is increased over consecutive bouts of tapping. Hansen, Ernst Albin; Rasmussen, Jakob; Ebbesen, Brian Duborg; Mora-Jensen, Mark Holten; Dalsgaard, Ane; Sardroodian, Mahta; Madeleine, Pascal.
27. Accelerated reading training improves reading fluency in Spanish speaking children. An eye-tracking study. Gomez-Velazquez, Fabiola; Gonzalez-Garrido, Andres; Garcia, Monica.
28. Influence of individual differences in impulsive action or impulsive choice on responding for a conditioned reinforcer and dopamine release. Zeeb, Fiona; Funk, Doug; Soko, Ashlie; Ji, Xiaodong; Fletcher, Paul.
29. Interplay between glutamatergic and cannabinoid systems within the dorsal periaqueductal gray matter modulates fear memory encoding and defensive behavior expression in an olfactory conditioning paradigm. Back, Franklin; Carobrez, Antonio.
30. Enhanced frontal cortex activity elicited by emotional stimuli in veterans with hazardous alcohol use and posttraumatic stress disorder. Forster, Gina, Olson, Dawne, Baugh, Lee, Hansen, Jamie, Engel, Shaydel, Simons, Raluca, Simons, Jeffrey, and Magnotta, Vincent.

31. Prenatal stress and acute stress later in life impacts the responses in tests for depressive-like behavior in a sex-specific manner. Sickmann, Helle M.; Skoven, Christian; Arentzen, Tina S.; Plath, Niels; Bastlund, Jesper F.; Dyrby, Tim B.; Kohlmeier, Kristi A.; Zhang Hui; Kristensen. Morten P.
32. Characterization of ketamine and selective NR2B antagonists in animal models predictive of antidepressant activity. Shoblock, James; Welty, Natalie; Lord, Brian; Azar, Marc; Willems, Roland; Ver Donck, Luc; Bonaventure, Pascal; Lovenberg, Tim; Balana, Bartosz; Chen, Guang.
33. Fluoxetine exposure during adolescence disrupts spatial memory performance in adulthood. Alipio, Jason B.; Cruz, Bryan; Shawhan, Kristi L.; Riggs, Lace M.; Iniguez, Sergio D.
34. Role of projections from ventral subiculum to nucleus accumbens shell and ventral medial prefrontal cortex in context-induced reinstatement of heroin seeking. Bossert, Jennifer M; Adhikary, Sweta; St. Laurent, Robyn M; Marchant Nathan J; Wang Hui-Ling; Morales, Marisela; Shaham, Yavin.
35. The Role of Behavioral Flexibility in Anxiety Vulnerability. Catuzzi, Jennifer; Beck, Kevin; Pang, Kevin.
36. The rapid effects of medial amygdalar and hippocampal G-protein coupled estrogen receptor on social recognition learning in female mice. Lymer, Jennifer; Blackman, Andrea; Barrett, Cassandra; Choleris, Elena.
37. Lack of depression-like phenotypes in C57BL-6J mice subjected to different types of chronic stressors. Jillian R. Hufgard, Michael T. Williams, and Charles V. Vorhees.
38. Inhibiting lactation increases depression-like behavior in postpartum rats. Workman, Joanna L.; Gobinath, Aarthi R.; Solomon, Sophia; Chow, Carmen; Galea, Liisa A.M.
39. The long-term, sex-dependent effects of adolescent social stress on depressive-like behavior and stress-related neurocircuitry. Lukkes, Jodi L.; Norman, Kevin J.; Meda, Shirisha; Andersen, Susan L.
40. Effect of chronic stress on markers of plasticity associated with mPFC mediated cognitive flexibility in rats. Jett, Julianne; Evans, Lauren; Morilak, David.
41. Stress affects response inhibition when emotional contexts are involved. Ramos-Loyo, Julieta, Briseño-Pulido, José Eduardo.
42. Changes in serotonin signaling alter multisensory function in the mouse: Implications for autism. Siemann, Justin; Muller, Christopher; Forsberg, Gunnar; Blakely, Randy; Veenstra-VanderWeele, Jeremy; Wallace, Mark.
43. The role of endogenous dynorphin in depression-like behaviors in C57/BL6 mice. Lutfy, Kabirullah; Hamid, Abdul; Marquez, Paul; Chan, Patrick.
44. Prenatal nicotine exposure impairs the proliferation of neuronal progenitors, leading to fewer glutamatergic neurons in the medial prefrontal cortex. Yamada, Kiyofumi; Aoyama, Yuki; Toriumi, Kazuya; Mouri, Akihiro; Hattori, Tomoya; Ueda, Eriko; Shimato, Akane; Sakakibara, Nami; Soh, Yuka; Mamiya, Takayoshi; Nagai, Taku; Kim, Hyoung-Chun; Hiramatsu, Masayuki; Nabeshima, Toshitaka.
45. Broadband local field potential characteristics in rat cingulate cortex are predictive of high-effort, goal-directed behaviour. Hillman, Kristin; Bilkey, David.
46. The effect of MMP-9 manipulation on social behavior. Meyza Ksenia, Kondrakiewicz Kacper, Ziegart-Sadowska Karolina, Nikołajew Tomasz, Puścian Alicja, Knapska Ewelina
47. The TNF- antagonist Enbrel produces reversals in forced-swim test and object memory deficits induced by repeated corticosterone administration in rodents. Brymer, Kyle; Caruncho, Hector; Kalynchuk, Lisa.
48. Organizational influences of sex steroid hormones on corticosteroid and glucocorticoid receptor responses in male and female Long Evan rats. Innala, Leyla; Yang, Yi; Anonuevo, Adam; Viau, Victor.
49. Anxiety vulnerable individuals exhibit enhanced classical eyeblink conditioning when trial timing is uncertain: support for a learning diathesis model of anxiety disorders. Allen, M. Todd; Myers, Catherine; Servatius, Richard.

50. Disinhibition of prefrontal cortex differentially gates hippocampal and amygdala inputs to the nucleus accumbens. Tse, Maric; Floresco, Stan.
51. Adolescent social defeat alters tyrosine hydroxylase activity in distinct cortical and subcortical regions of the young adult brain. Weber, Matthew A.; Scholl, Jamie L.; Paulson, Riley T.; Forster, Gina L.; Renner, Kenneth J.; Watt, Michael J.
52. Prefrontal GABA-A and NMDA receptor modulation of working memory assessed with a delayed non-match to position task. Auger, Meagan; Floresco, Stan.
53. “Gut feelings”: Vagal afferent signaling modulates behavioral flexibility in rats. Klarer, Melanie; Arnold, Myrtha; Krieger, Jean-Philippe; Langhans, Wolfgang; Meyer, Urs.
54. Inactivation of the orbitofrontal cortex reduces irrational choice on a rodent Betting Task. Barrus, Michael M.; Hosking, Jay G.; Cocker, Paul J.; Winstanley, Catherine A.
55. Cortical circuitry underlying emotional memory to predatory threats. De Lima, Miguel Antonio Xavier; Canteras, Newton Sabino.
56. Interactions of behavioral training and ketamine administration on changes in parvalbumin positive neurons. Monica M. Bolton, Chelcie F. Heaney, Andrew S. Murtishaw, Jefferson W. Kinney.
57. Assessing the treatment predictive validity of model animals of bipolar mania. Milienne-Petiot, Morgane; Enkhuizen van, Jordy; Geyer, Mark A; Young, Jared W.
58. Does sleep play a role in event cued prospective memory? Exploring the role of cue encodings. Singh, T; Kashyap, N.
59. D1/D2 receptor modulation of risk/reward decision-making in prefrontal-subcortical circuits. Jenni, Nicole; Larkin, Josh; Floresco, Stan.
60. The effect of minocycline pre-treatment on nicotine-induced alterations during periadolesence of neuronal ΔFosB expression in limbic areas of the rat brain. Nagchowdhuri, Partha S.; Lane, Kristen T.; Williams, Helen L.; McMillen, Brian A.
61. Impact of CRHR1 blockade on BDNF and TrkB immunohistochemical expression in the hippocampus, amygdala and hypothalamus: relationship to spatial memory and fear learning following global cerebral ischemia in rats. Patricia B. de la Tremblaye, Simon Benoit, Hélène Plamondon.
62. Depressive-like behavior in mice lacking the low-density lipoprotein receptor. Brocardo PS; Engel D; Rodrigues ALS; de Bem AF.
63. Chronic administration of the D2-like agonist ropinirole galvanises behaviour on a rodent slot machine task: Toward a rodent model of problem gambling. Cocker, Paul John; Tremblay, Melanie; Winstanley, Catharine Antonia.
64. Organic cation transporter 3 is expressed on neurons and glia in the amygdala: A mechanism for stress-induced modulation of amygdala activity. Hill, Jonathan; Chan, Joan; Hurley, Matthew; Pickel, Virginia; Gasser, Paul.
65. Immunization with the immunoregulatory saprophytic bacterium, Mycobacterium vaccae, enhances fear extinction in adult male Sprague Dawley rats. Siebler, Philip; Fox, James; Hassell, James; Lowry, Christopher.
66. Age-related changes in frailty in two mouse models of Alzheimer’s disease. Brown, Richard E. and Shin Sooyoun.
67. Age-related cognitive changes in 3xTg and 5xFAD mice: assessment using touchscreen-based automated tasks. Winters, Boyer; Palmer, Daniel; Creighton, Samantha; Wasserman, David; Thorne, Meghan; Schubert, Jocelyn; Beraldo, Flavio; Masood, Talal; Cowan, Matthew; Prado, Vania; Prado, Marco.
68. The role of hippocampal dopamine D2-type receptors in the social transmission of food preferences in male and female mice. Matta, Richard; Underwood, Emily A.; Leach, Zoe K.; Vertes, Alex C.; Choleris, Elena.
69. Increased neuronal density in CA1, locomotion and levels of estradiol in presence of a bee products in postmenopausal rats. Mayen Díaz Rodrigo, Vázquez Matías Daniel Aarón, Zarraga Galindo Norma, Sanchez Cervantes Ivonne Grisel, López Martínez Irma, Fragoso Alcalá Elvis,

Martinez Tapia Ricardo ,Velázquez Paniagua Mireya, Ramírez Escoto Marcela, Vergara Aragón Patricia.

70. Dissociable contributions of maintenance and de novo DNA methyltransferases to object and spatial memory in the rat perirhinal cortex and hippocampus. Creighton, Samantha; Mitchnick, Krista; AlIzzi, Amina; Kalisch, Bettina; Winters, Boyer.
71. Play it again, Sam: An investigation of rough-and-tumble play on neurobiological and cardiovascular markers of emotional regulation in rats exposed to repeated stressors. Scott, Samantha; Kent, Molly; Bardi, Massimo; Lambert, Kelly.
72. Phenotyping emotional resilience: Flexible coping strategies align with adaptive neurobiological responses to prediction errors and challenge tasks in male and female rats. Kent, Molly; Hazelgrove, Ashley; Sewell, Kaitlyn; Kirk, Emily; Thompson, Brooke; Lambert, Skylar; Trexler, Kristen; Terhune-Cotter, Brennan; Bardi, Massimo; Lambert, Kelly.
73. C-Fos expression of anxiolytic effects of benzodiazepines in prefrontal cortex of rats. S.E. Cruz-Morales, D. J. Gonzalez-Sanchez, G. Castillo-Roberto.
74. Scorpion Venom Heat-Resistant Peptide (SVHRP) treatment rescues deficits in learning and memory of APP/PS1 transgenic model mice of Alzheimer disease. Shao, Li; Jin-Yi, Yang; Guang, Yang; Jian-Jiao, Chen; Tao, Wang; Yan, Peng; Wan-qin, Zhang; Jie,Zhao.
75. Postnatal stress induced by injection with valproate leads to developing emotional disorders along with molecular and cellular changes in the hippocampus and amygdala. Wang, Chih-Yen; Wang, Wei-Hua; Cheng, Chien-Wen; Chen, Po-See; Tzeng, Shun-Fen.
76. Reversal of effect in the novel object recognition (nor) test in the presence of an external olfactory stimuli. Alumri, Talal; Greengrass, Colin; Zhu, Yi Zhun.
77. Fear and fear extinction learning in APP/PS1 mice. Endres, Thomas; Hölzl, Gloria; Caglayan, Alican; Lessmann, Volkmar; Edelmann, Elke.
78. A glycine receptor subunit homologue, AVR-14, alters short-term memory in an interstimulus interval-dependent manner in *C. Elegans*. McDiarmid, Troy; Ardiel, Evan; Rankin, Catharine.
79. Prenatal alcohol exposure increases anxiety-like behavior in males but depressive-like behavior in females two weeks following chronic unpredictable stress. Lam, Vivian Y.Y.; Takeuchi, Lily; Raineki, Charlis; Weinberg, Joanne.
80. Effects of osmotic and non-osmotic stimuli on drinking behavior in TRPV1 and TRPV4 knockout mice. Yoichi, Ueta; Takanori, Matsuura; Yasuhito, Motojima; Mitsuhiro, Yoshimura; Kanako, Shoguchi; Takashi, Maruyama; Hirofumi, Hashimoto; Makoto, Kawasaki; Hideo, Ohnishi; Akinori, Sakai.
81. Activation of Adenosine A2A receptors exacerbates cognitive dysfunction induced by traumatic brain injury by promoting hyperphosphorylation of the C-terminal of Tau protein. Yuanguo, Zhou; Ziai, Zhao; Ping, Li; Yalei, Ning; Nan, Yang; Yan, Peng; Yan, Zhao; Xingyun, Chen; Xing, Chen; Wei, Bai; Xujia,Zeng.
82. Lutein dietary supplementation inhibited the oxidative and inflammatory biomarkers in the brain of diabetic rats. Khaled A. Al-Hosaini, Abdulaziz S. Alroujaee, Abdulaziz Y. Alturki, Amal J. Fatani.
83. Stress increases sucrose intake in binge eating prone female rats. De Avila Camila, Calvez Juliane, Timofeeva Elena.

Thursday, June 4

8:00-10:00 **Neuroadaptations to chronic antipsychotic treatment in preclinical models.** Chair: **Anthony Vernon, Margret Hahn.** *Oak Bay Rooms*

8:00 Presynaptic adaptations associated to a gradual loss of antipsychotic efficacy. Amato, Davide.

8:30 Impact of chronic antipsychotic drug treatment on brain morphology: a cause for concern? Anthony Vernon.

9:00 Preclinical modeling of antipsychotic-related metabolic side-effects: a viable approach? Hahn, Margaret; Chintoh, Araba; Giacca, Adria; Mann, Steve; Remington, Gary.

9:30 Post-mortem studies in schizophrenia: accounting for antipsychotics. Beasley, Clare L.

8:00-10:00 **Neurogenesis: Sex, drugs and memory – what's neurogenesis have to do with it?** Chairs: **Brian Christie, Liisa Galea.** *Lecture Theatre*

8:00 Stress-dependent functions for adult hippocampal neurogenesis in learning and memory. O'Leary, Timothy; Snyder, Jason.

8:30 The impact of sex, drugs and heavy metal on adult hippocampal neurogenesis. Dyck, Richard; Chrusch, Michael; Boon, Jacqueline; Spanswick, Simon; Vecchiarelli, Haley; Hill Matthew.

9:00 Stressed and Depressed: How sex modifies the relationship to hippocampal neurogenesis. Galea, Liisa A.M.

9:30 Ambient temperature influences the neural benefits of exercise. Leasure, J. Leigh; Maynard, Mark; Chung, Chasity; Comer, Ashley; Nelson, Katharine; Tran, Jamie; Werries, Nadja; Barton, Emily; Spinetta, Michael.

10:30 **Keynote: Jaak Panksepp**, Bowling Green State University, Bowling Green, OH, USA. Affective neuroscience psychiatric perspectives on primal emotional feelings in other animals: Are their affects homologous to our own? *Lecture Theatre*

11:30-1:00 **Meet the Professionals: Career Development Event**

A career development event for student and postdoctoral trainees to network with professionals who have applied their PhD's in biomedical research to a diverse range of career paths (e.g., academic research, education, industry, public outreach, law, administration, advocacy, military/government research, etc.).

Trainees interested in participating in this event are asked to RSVP at the IBNS Registration Desk, the Student/Postdoctoral Social, the Opening IBNS Reception, or by emailing the IBNS Council Student Representative, Julianne Jett (jettj@uthscsa.edu).

Trainees and professionals will convene at the IBNS Registration Desk then head to lunch at a location close to the meeting (we provide a list of convenient restaurants and trainees pay for their own meal).

1:00-3:00 **Understanding the mechanism of behavioral flexibility and its role in cognition and abnormal behavior.** Chair: **Jennifer Catuzzi.** *Lecture Theatre*

1:00 Translational approach to understanding behavioral inflexibility in autism. Ragozzino, Michael; Amodeo, Dennis.

1:24 Effect of anxiety on spontaneous activity of the prefrontal cortex and its neuronal correlates of the extra-dimensional set-shifting. Moghaddam, Bita; Park Junchol.

1:48 Shifts in prefrontal cortical excitatory/inhibitory dynamics in aging: implications for cognition. Jennifer L. Bizon.

2:12 Exercise effects on behavioral flexibility and prefrontal cortex in adult and adolescent rats. Green, John T.; Eddy, Meghan C.

2:36 The Role of Behavioral Flexibility in Anxiety Vulnerability. Catuzzi, Jennifer; Beck, Kevin; Pang, Kevin.

1:00-3:00 **What do rodent ultrasonic vocalizations reveal about brain function, affective states and communication?** Chair: **Paul B.S. Clarke.** *Oak Bay Rooms*

1:00 Ultrasonic vocalization and emotional arousal systems. Stefan M. Brudzynski.

1:30 Neurobiological factors involved in production and perception of pro-social 50-kHz ultrasonic vocalizations in rats. Wöhr, Markus.

2:00 Adult rat 50-kHz ultrasonic vocalizations as potential indicators of emotional state. Clarke, Paul.

2:30 Ultrasonic vocalizations as motivational and emotional markers during social interactions in mice. Granon, Sylvie; Cressant, Arnaud; Chauveau, Frédéric; Pittaras, Elsa; Faure, Alexis.

3:30-5:30 **Inhibition and reward: Are they related?** Chairs: **Harriet de Wit, David Jentsch.** *Lecture Theatre*

3:30 Stop in the name of DRD2! Stop in the name of DRD2! Linking inhibition and reward through genetics. J. David Jentsch.

4:00 Reward valuation in withdrawal and abstinence: Roles of striatal D2 and BDNF. Alicia Izquierdo.

4:30 I can't stop myself, I like it: Inhibition and drug reward. de Wit, Harriet; Weafer, Jessica.

5:00 Right inferior frontal gyrus and the suppression of motor and reward processes. Garavan, H.

3:30-5:30 **Seeing through the smoke: Human and animal studies of cannabis use and endocannabinoid signalling in corticolimbic networks.** Chairs: **Iain McGregor, Wendy Adams.** *Lecture Theatre*

3:30 Physiological and neural adaptations following chronic cannabis use and implications for withdrawal. McGregor, I.

4:00 Sterol carrier protein-2 selectively regulates endocannabinoid signalling in the amygdala. Hillard, Cecilia.

4:30 Hippocampal cannabinoid transmission modulates mesolimbic neuronal activity states and regulates emotional processing and social cognition: Implications for schizophrenia. Steven R. Laviolette.

5:00 THC decreases cognitive effort without impairing attentional processes: The role of the cannabinoid system in a distinct form of cost/benefit decision-making. Silveira, M.M; Adams, W.K; Winstanley, CA.

6:00-6:30 **Early Career Award.** Introduction: **Stephen Kent** *Lecture Theatre*

Corina Bondi, University of Pittsburgh, PA, USA. Unraveling frontal lobe dysfunction after traumatic brain injury using preclinical models.

6:30-8:30 Oral Session 1. Chair: **Matthew Hale** *Lecture Theatre*

6:30 Systemic modulation of dopamine D2/D3 receptors revert orbitofrontal neurophysiological neural correlates of risk preference in a rodent gambling task of decision-making under uncertainty. Galhardo, Vasco; Cardoso-Cruz, Helder; Monteiro, Clara; Dourado, Margarida.

6:45 Chronic stress and ablation of neurogenesis independently reduce hippocampal volume. Schoenfeld, Timothy; McCauseland, Hayley; Cameron, Heather.

7:00 Neurochemical and behavioral comparison of contingent and non-contingent methamphetamine exposure using binge and long-access yoked self-administration paradigms. Keck, Thomas M.; Schweppe, Catherine; Burzynski, Caitlin; Ladenheim, Bruce; Cadet, Jean Lud; Gardner, Eliot L.; Xi, Zheng-Xiong Xi; van Praag, Henriette; Newman, Amy H.

7:15 Exploration of the role of GTF2i in the social phenotypes of Williams Beuren Syndrome and Autism Spectrum Disorder. Martin, Loren; Iceberg, Erica; Rahman, Megan; Lum, Breanna; Patterson, Amy.

7:30 The role of endogenous nociceptin in anxiety-like behaviors in C57/BL6 mice. Perez, Sidney; Marquez, Paul; Hamid, Abdul; Lutfy, Kabirullah.

7:45 Pharmacological assessment of a role for orbitofrontal adrenoreceptors in yohimbine-induced enhancement of motor impulsivity. Adams, Wendy K; Zeeb, Fiona D; Cocker, Paul J; Barrus, Michael M; Benoit, James; Winstanley, Catharine A.

8:00 Limbic neuropeptide y-1 receptors modulate vulnerability to social and metabolic challenges depending upon gender and maternal care. Palanza, Paola; Paterlini, Silvia; Panelli, Riccardo; Gioiosa, Laura; Parmigiani, Stefano; Mele, Paolo; Longo, Angela; Eva, Carola.

6:30-8:30 Oral Session 2: Chair: **Cliff Summers** *Oak Bay Rooms*

6:30 The effect of embryonic alcohol exposure on social behaviour and underlying biological mechanisms in zebrafish. Mahabir, Samantha; Chatterjee, Diptendu; Gerlai, Robert.

6:45 Environmental Enrichment Reverses Transgenerational Programming by Early Trauma. McCreary, J. Keiko; Erickson, Zachary T.; Babenko, Alena; Ilnytskyy, Yaroslav; Olson, David M.; Kovalchuk, Igor; Metz, Gerlinde A.S.

7:00 Localization of phosphorylated AKT in VTA GABA neurons after social stress exposure: Functional implications for stress-induced amphetamine cross-sensitization in rats. Nikulina EM, Johnston CE, Hammer RP, Jr.

7:15 Sodium butyrate increases contextual fear expression in sign- but not goal-trackers. Fitzpatrick, Christopher J.; Wood, Marcelo A.; Morrow, Jonathan D.

7:30 Mice smell their neighbors' increased pain. Smith, Monique L; Hostetler, Caroline M.; Li, Ju; Heinricher, Mary M; Ryabinin, Andrey.

7:45 Cholinergic contributions to prefrontal load and attentional capacity in aging. Yegla, Brittney; Francesconi, Jennifer; Parikh, Vinay.

8:00 Cross-modulation of cholinergic and GABAergic signaling at the NMJ and resultant effects on C. elegans mobility. Rose, Jacqueline; Stafford, Parker; Stankowicz, Nicole; Leonti, Amanda; Mar, Katrina; Moss, Samuel; Records-Galbraith; Andrew.

8:15 Lipopolysaccharide-induced inflammation increases the expression, but not extinction, of conditioned fear. Young, Matthew B.; Howell, Leonard L.

Friday, June 5

8:00-10:00 **Research Domain Criteria versus DSM V: How does this debate affect attempts to model corticostriatal dysfunction in animals?** Chair: **F. Scott Hall.** *Oak Bay Rooms*

8:00 Reducing dopamine transporter expression in mice recreates a mania-like behavioral profile. Young, Jared; Minassian, Arpi; Milienne Petiot, Morgane; Perry, William; Geyer, Mark.

8:30 Dopamine transporter knockout mice as an animal model of attention deficit hyperactivity disorder. Hall, F. Scott.

9:00 Chronic dopamine agonist treatment: An animal model of vulnerability to pathological gambling? Winstanley, Catharine.

9:30 Modelling corticostriatal dysfunction in schizophrenia. Brady, Anne Marie.

8:00-10:00 **Impact of adolescent social experiences on behavior and neural circuits relevant to mental illnesses.** Chair: **Jodi Lukkes, Andrew Burke.** *Lecture Theatre*

8:00 The role of the cortex in the evolution of social play. Pellis, Sergio.

8:30 Social defeat during adolescence escalates adult cocaine self-administration: Role of adolescent social experience and adaptive coping behaviors. Burke, Andrew R.; Miczek, Klaus A.

9:00 Social and hormonal factors in differences in stress responses between adolescents and adult rats. McCormick, Cheryl.

9:30 The long-term, sex-dependent effects of adolescent social stress on depressive-like behavior and stress-related neurocircuitry. Lukkes, Jodi L.; Norman, Kevin J.; Meda, Shirisha; Andersen, Susan L.

10:30 **Bench-to-Bedside Lecture: J.F. William Deakin**, University of Manchester, U.K. Finding new treatments for schizophrenia; behavior, biomarkers and clinical trials. *Lecture Theatre*

1:00-3:00 **Obsessive-compulsive disorder: Insights from animal models.** Chair: **Henry Szechtman; Richard Beninger.** *Oak Bay Rooms*

1:00 Understanding the OCD brain: Using new technologies to build bridges between mice and humans. Ahmari, Susanne E.

1:24 Mechanisms of polydipsia in rats: Clues for understanding OCD. Beninger, Richard J; Hawken, Emily R.

1:48 The deer mouse model of obsessive-compulsive disorder (OCD): A platform for research in neurobiology, behaviour and drug discovery. Harvey, Brian.

2:12 Analysis and synthesis of compulsive checking: Indications that OCD is a disturbance of motivation. Szechtman, Henry.

2:36 Discovering macroscopic networks and their modulation in animal models of repetitive disorders. Christine Winter.

1:00-3:00 **Why sex hormones matter for behavior and brain health.** Chairs: **Elena Choleris, Liisa Galea.** *Lecture Theatre*

1:00 Estrogens and the aging brain: Maintenance functions of sex steroids in the female frontal cortex. Hampson, Elizabeth.

1:24 Molecular mechanisms underlying estrogenic memory enhancement. Frick, Karyn M.

1:48 Rapid action of estrogens and their receptors in the brain: Implications for learning. Choleris, Elena; Phan, Anna; Lymer, Jennifer; Ervin, Kelsy; Gabor, Christopher.

2:12 Stroke neuroprotection in aging females: Beyond estrogen. Sohrabji, Farida.

2:36 Caveats and pitfalls for studying the influence of sex and sex hormones in neuroscience. Galea, Liisa A.M.

3:30-5:30 **Standardization of Rodent Behavioral Testing: Where we've been, and where we're going.** Chair: **Abbe H. Macbeth.** *Lecture Theatre*

3:30 Standardized Assays for Mouse Models of Neurodevelopmental Disorders. Silverman, J.L.

4:00 You want me to do what with your mouse? Tales of "standardized testing" from the behavioral testing core facility at UCSD. Heyser, C.

4:30 Motherhood in many contexts: Standardization of maternal behavior testing. Stolzenberg, D.S.

5:00 "Standardized" tests and the problem of reliability and validity in mouse behavioural bioassays. Brown, R.E.

3:30-5:30 **Neurobiological consequences of drug exposure during adolescence: Mechanisms and long-term effects.** Chairs: **Arturo R. Zavala, Sergio D. Iñiguez.** *Oak Bay Rooms*

3:30 Juvenile administration of concomitant methylphenidate and fluoxetine alters behavioral reactivity to reward and aversive stimuli and disrupts ventral tegmental area gene expression in adulthood. Bolanos-Guzman, Carlos A.; Alcantara, Lyonna F.; Parise, Eric M.; Sial, Omar K.

3:55 Adolescent prescription drug exposure effects on social play behavior and frontal cortex-dependent reward learning. Izquierdo, Alicia.

4:20 Neurobiological consequences of nicotine exposure during adolescence: Short and long-term effects. Laura E. O'Dell, Luis A. Natividad, Luis Carcoba.

4:45 Amphetamine in adolescence disrupts prefrontal cortex development. Flores, Cecilia.

5:10 Janet L. Neisewander. Discussant.

6:00-8:00 **Poster Session 2** *Saanich Rooms and Pre-Function Area*

1. Perturbations in prefrontal-ventral striatal mediated cognitive functions, dopaminergic innervation and testosterone associated with aging. Tomm, Ryan; Ma, Cathy; Low, Katelyn; Tse, Maric; Grist, Madison; Floresco, Stan; Soma, Kiran.
2. Behavioral effects of inactivating DA receptors in the caudate-putamen and nucleus accumbens of young rats. Mohd-Yusof, Alena; Rudberg, Krista; Moran, Andrea; Razo, Jessica; Macedo, Evelyn; Eaton, Shannon; Crawford, Cynthia; McDougall, Sanders.
3. Behavior features and response to naltrexone among outbred Wistar rats from different suppliers. Shima Momeni; Lova Segerström; Erika Roman.
4. Systemic modulation of dopamine D2/D3 receptors revert orbitofrontal neurophysiological neural correlates of risk preference in a rodent gambling task of decision-making under uncertainty. Galhardo, Vasco; Cardoso-Cruz, Helder; Monteiro, Clara; Dourado, Margarida.
5. Assessing the effects of light dark manipulation and caffeine exposure on zebrafish sleep behavior. Khan, Kanza; Lodinger, Natalie; Collier, Adam; Caramillo, Erika; Echevarria, David.
6. The microbiota regulates amygdaloid volume and dendritic length. Pauline Luczynski, Gerard Clarke, Fergus Shanahan, Timothy G. Dinan, John F. Cryan.
7. From reward prediction error to dopamine hypothesis of psychosis: Insights from Akt1 mutant mice and schizophrenic patients. Lai, Wen-Sung; Chen, Ching; Liu, Hung-Hsiang; Liu, Ya-Wen; Li, Chia-Tzu; Chen, Yao-Chu; Liu, Chih-Ming; Hsu, Yung-Fong.
8. Valproic acid improves anxiety-like behavior and amphetamine hyper-reactivity in isolation reared trait anxiety rats but reverses the benefits of environmental enrichment. Donaldson, S. Tiffany; Buteme, Juliet; Romero, Vanessa; Lusse, Joseph.
9. Social buffering enhances extinction of fear response in male rats. Yasushi Kiyokawa, Kaori Mikami, Yukari Takeuchi, and Yuji Mori.
10. Establishing a role for cortico-thalamic circuitry in cue-driven behaviors. Haight, Joshua; Fraser, Kurt; Akil, Huda; Ferguson, Susan; Flagel, Shelly.
11. Differential effects of Resveratrol on the expression of BDNF transcripts and protein in the hippocampi from adult and embryonic rat brain. Shojaei, Shahla; Panjehshahin, Mohammad Reza; Shafiee, Mohammad; Khoshdel, Zahra; Borji, Mohammad; Ghasempour, Ghasem; Owji, Ali Akbar.
12. Vaginal and uterine absorption of estradiol from male seminal emissions during mating in mice. Pollock, Tyler; deCatanzaro, Denys.
13. A novel task to assess reversal learning in mice in a home-cage environment. Remmelink, Esther; Verhage, Matthijs; Smit, August B.; Loos, Maarten.
14. Emotional aspects of event learning in rats: Characterization and neural basis. Bergado-Acosta, Jorge R.; Brosch, Marcel; Bruning, Johann; Mohammadi, Milad; Uzuneser, Taygun; Fendt, Markus.
15. Behavioral and Hormonal changes in male and female rats due maternal separation during breastfeeding. Dueñas Zulma, Riveros-Barrera Irene, Caicedo-Mera Juan Carlos, Laura J Martín.
16. Individual differences in human susceptilibity to alpha-band EEG entrainment induced by photic stimulation. Cocchieri, Caterina; Thalheimer, William; Ashman, John; Storrs, Tyler; Foster, Vance; Vevi, Elizabeth; Langford, William; Saia, Dominic; Flores, Juan; Flores, Marylinda; Danbury, Michelle; Cetrulo, Gabrielle; Rossi III, John.
17. Are standard laboratory animals more stress-sensitive? Ashokan, Archana; Mitra, Rupshi.
18. Enriched environment: A resilience-inducer involving BDNF modulation. Hegde, Akshaya; Mitra, Rupshi.
19. Involvement of orexin in the sex-specific effect of relaxin-3 on food intake in rats. Calvez, Juliane; Lenglos, Christophe; De Avila, Camila; Timofeeva, Elena.

20. Prolonged maternal separation affect corticosterone levels and social play behavior in adolescent male but not female Wistar rats. Lundberg, Stina; Martinsson, My; Nylander, Ingrid; Roman, Erika.
21. Control of the septohippocampal pathway and learning and memory by relaxin-3/RXFP3 neural networks: Viral-based studies in transgenic mice. Haidar, Mouna; Hawkes, David; Guevremont, Genevieve; Olucha-Bordonau, Francisco; Ma, Sherie; Bathgate, Ross; Timofeeva, Elena; Smith, Craig; Gundlach, Andrew.
22. Most people use both allocentric and egocentric strategies to solve a dual-strategy virtual Morris water maze. Ferguson, Thomas; van Gerven, Dustin; Skelton, Ronald.
23. Signaling by tuberoinfundibular peptide of 39 residues in the medial amygdala modulates remote fear memory. Tsuda, Mumeko C; Usdin, Ted B.
24. Regulation of discriminative fear conditioning by prefrontal and striatal subregions. Piantadosi, Patrick; Yeates, Dylan; Floresco, Stan.
25. Role of striatal cholinergic interneurons in set-shifting in the rat. Aoki, Sho; Liu, Andrew; Zucca, Aya; Zucca, Stefano; Wickens Jeffery.
26. Sex Differences in the Acquisition of Conditioned Disgust Behaviour in the rat. Cloutier-Duke, Caylen J; Kavaliers, Martin; Ossenkopp, Klaus-Peter.
27. Discovering macroscopic networks and their modulation in animal models of repetitive disorders. Christine Winter.
28. Social factors modulate toxin-induced disgust responses in rats. Boulet, Nathalie; Kavaliers, Martin; Ossenkopp, Peter; Cloutier, Caylen.
29. The role of corticotropin-releasing factor in mediating the effect of acute stress on effort-based decision-making. Bryce, Courtney; Floresco, Stan.
30. Mother rats know best: An investigation of maternal experience on cognitive and emotional resilience. Kirk, Emily; Kent, Molly; Hazelgrove, Ashley; Bardi, Massimo; Lambert, Kelly.
31. Sex differences in two tests of anxiety-like behavior in rats. Scholl, J.L., Fox, L.C., Watt, M.J., Forster, G.L.
32. Methylene blue enhances mitochondrial activity, functional connectivity and memory performance in rats experiencing chronic cerebral hypoperfusion. Auchter, Allison; Gonzalez-Lima, Francisco; Monfils, Marie.
33. Motoric and automated home cage assessment of a transgenic rat model of spinocerebellar ataxia type 17 (SCA17). Elisavet I. Kyriakou, Johanneke E. van der Harst, Andrew J. Spink, Huu P. Nguyen, Judith R. Homberg.
34. Consequences of two different periods of neonatal maternal separation on social behavior of adolescent male rat. Magalhaes, Ana; Nogueira, Marlene; Alves, Cecilia Juliana; Mesquita, Ana; Summavielle, Teresa; de Sousa, Liliana.
35. Individual differences in locomotor activity correlate with behavioral responses to ethanol in zebrafish: Potential roles of the dopaminergic and serotonergic neurotransmitter systems. Tran, Steven; Nowicki, Magda; Muraleetharan, Arrujyan; Chatterjee, Diptendu; Gerlai, Robert.
36. A novel object recognition task that leads to a lasting expression of memory. Michael J. Spinetta, Jessica I. Wooden, Mark E. Maynard, Charles I. O'Leary, J. Leigh Leasure.
37. Effects of aging on testosterone and androgen receptors in the male rat forebrain. Low, Katelyn; Ma, Chunqi; Tomm, Ryan; Tse, Maric; Grist, Madison; Floresco, Stan; Soma, Kiran.
38. Sexual interactions among rats: Who takes the initiative? Agmo, Anders; Bergheim, Dag; Chu, Xi.
39. Acetylcholine signaling at muscarinic receptors is necessary for social learning in female mice. Ervin, Kelsy; Sawula, Melanie; Paletta, Peter; Choleris, Elena.
40. A change of heart: Mapping coping style phenotypes to cardiovascular and neurobiological responses associated with emotional regulation in male and female rats (*Rattus norvegicus*). Thompson, Brooke; Kent, Molly; Kirk; Emily; Bardi, Massimo; Lambert, Kelly.
41. Subtypes of prefrontal cortical NDMA receptors in working memory and normal aging. McQuail, JA; Beas, BS; Simpson, K; Setlow B; Bizon, JL.

42. Exploration of the role of GTF2i in the social phenotypes of Williams Beuren Syndrome and Autism Spectrum Disorder. Martin, Loren; Iceberg, Erica; Rahman, Megan; Lum, Breanna; Patterson, Amy.
43. Cognitive impairments in a mouse model of 16p11.2 deletion syndrome. Mu Yang, Freeman Lewis, Gillian Foley, Jacqueline N. Crawley.
44. Investigation of dual orexin receptor antagonism on cocaine reward and initial positive affective reactivity to cocaine in rats. Simmons, Steven J.; Gentile, Taylor A.; Barker, David J.; Muschamp, John W.
45. Dopamine agonist ropinirole medication increases gambling behaviours in a 6-OHDA rat model of Parkinson's disease. Tremblay, Melanie; Silveira, Mason; Adams, Wendy; Winstanley, Catharine.
46. Involvement of PI3K/Akt signaling pathway and its downstream intracellular targets in the antidepressant-like effect of creatine. Cunha, Mauricio; Budni, Josiane; Ludka, Fabiana; Pazini, Francis; Rosa, Julia; Oliveira, Agatha; Tasca, Carla; Rodrigues, Ana Lucia.
47. Decreased anxiety and enhanced fronto-hippocampal connectivity in the Prrxl1 knockout mouse model of congenital hypoalgesia. Monteiro, Clara; Cardoso-Cruz, Helder; Dourado, Margarida; Lima, Deolinda; Galhardo, Vasco.
48. Impact of adolescent ethanol exposure and adult amphetamine self-administration on evoked striatal dopamine release in rats. Granholm, Linnea; Rowley, Samuel; Ellgren, Maria; Segerström, Lova; Nylander, Ingrid.
49. Effects of early-life adversity and prenatal alcohol exposure on object recognition memory in male and female adolescent rats. Holman, Parker J.; Haghighat, Sepehr; Raineki, Charlis; Weinberg, Joanne.
50. Early appearance of cognitive impairment in a mouse model of depression is associated with altered synaptic plasticity and enhanced hippocampal GluA1 expression. Izhak Michaelevski, Moshe Gross, Anton Shenina, Elimelech Nesher, Tatiana Tikhonov, Danny Baranes, Albert Pinhasov.
51. Cystatin F gene ablation exacerbates the status of demyelination in cuprizone model mice. Junjie Liang, Ning Li, Kai Fan, Yanli Zhang, Ikenaka Kazuhiro, Jianmei Ma.
52. Involvement of opioid signaling in food preference and effort-related decision making in rats. Morales, I.; Brockway, E.; Selva, J.; Baumgartner, H.; Zallar, L.; Currie, P.; Hackenberg, T.; Pastor, R.
53. An animal model of recurrent depression: Investigating potential mechanisms of depressive episode recurrence. Katherina Lebedeva, Erin Fenton, Rudy Bowen, Hector Caruncho, Lisa Kalynchuk.
54. Obesity and binge eating are associated with heightened negative affect and desire to eat, but not hunger, following mental stress: Preliminary evidence. Klatzkin, Rebecca; Gaffney, Sierra; Madigan, LauraLee; Sumner, Caroline; Baldassaro, Allie; Rashid, Saniya.
55. Effect of DREADD-mediated inhibition of G-protein coupled signaling in lateral habenula neurons on operant cocaine or food self-administration and reinstatement in rats. Nair, Sunila; Smirnov, Denis; Neumaier, John.
56. Role of nucleus accumbens core (NAc) in the modulation of motor vigor with mCPP: Implications for the quinpirole sensitization rat model of obsessive-compulsive disorder (OCD). Tucci, Mark C; Dvorkin-Gheva, Anna; Johnson, Eric; Szechtman, Henry.
57. Dose-dependent effects of amphetamine, atomoxetine and amantadine on cognitive outcome following traumatic brain injury in rats. Lam, Frederick C.W.; Vonder Haar, Cole; Winstanley, Catharine A.
58. Neuroanatomical correlates of speech production in normal aging and mild Alzheimer's disease. Rodriguez-Aranda, Claudia; Waterloo Knut; Johnsen, Stein Harald; Eldevik, Peter; Sparr, Sigurd; Wikran, Gry; Herder Marit; Vangberg, Torgil.
59. Effects of adenosinergic drugs on contextual fear conditioning, social interaction and locomotion in an animal model of schizophrenia. Ramos, Aline Camargo; Camerini, Bianca Avansi; Gouvêa,

Douglas Albuquerque; Derci, Neide; Vendramini, Ana M.; Suiama, Mayra A.; Abílio, Vanessa Costeck; Calzavara, Mariana Bendlin.

60. Investigation of stressor controllability on anxiety-like behaviors in mice. Burrow, Kristin Rasmus; Hood, Jordan; Maier, Steve; Ehringer, Marissa.
61. Intrahippocampal infusions of the extracellular matrix glycoprotein reelin ameliorates fear memory impairment associated with kindling of the basolateral amygdala. Botterill, Justin; Ferguson, Daniel; Caruncho, Hector; Kalynchuk, Lisa.
62. Multigenerational prenatal stress leads to emotional disturbances and altered neuroanatomical pathology of the medial prefrontal cortex (mPFC). Ambeskovic, Mirela; Falkenberg, Erin; Kolb, Bryan; Metz, Gerlinde.
63. Witness defeat: A novel animal model of vicarious stress-induced depression in female c57BL/6 mice. Riggs, Lace M; Alipio, Jason B; Hernandez, Mirella A; Flores-Ramirez, Francisco J; Iniguez, Sergio D.
64. Lipopolysaccharide-induced inflammation increases the expression, but not extinction, of conditioned fear. Young, Matthew B.; Howell, Leonard L.
65. Long-term ovariectomy increases vulnerability to chronic stress and modulates the effects of fluoxetine on hippocampal plasticity. Mahmoud, Rand; Wainwright, Steve; Chaiton, Jessica; Lieblich, Stephanie; Galea, Liisa.
66. Chronic minocycline treatment rescues social behavioral deficit in male Fmr1 KO mice. Yau, Suk-Yu; Chiu, Christine; Vetrici, Mariana; Christie, Brian R.
67. Targeted GABA(A) pharmacotherapy in a mouse model of Fragile X Syndrome. Schaefer, Tori L; Ashworth, Amy A; Davenport, Matthew H; Stegman, Melinda S; Erickson, Craig A.
68. Neonatal (+)-methamphetamine exposure impairs egocentric learning in the Cincinnati water maze (CWM) and working memory in the radial water maze (RWM) in rats. Jablonski, Sarah; Gutierrez, Arnold; Tee, Trisha; Suttling, Kathryn; Williams, Michael; Vorhees, Charles.
69. Limbic neuropeptide y-1 receptors modulate vulnerability to social and metabolic challenges depending upon gender and maternal care. Palanza, Paola; Paterlini, Silvia; Panelli, Riccardo; Gioiosa, Laura; Parmigiani, Stefano; Mele, Paolo; Longo, Angela; Eva, Carola.
70. The role of pituitary adenylyl cyclase activating polypeptide in nicotine-induced aversion in C57/BL6 mice. Singh, Prableen; Tseng, Andy; Hamid, Abdu; Marquez, Paul; Lutfy, Kabirullah.
71. Activation and inhibition of oxytocin neurons via designer receptors. Curry, Daniel; Young, Matthew; Howell, Leonard.
72. Taurine modulates the effects of ethanol on zebrafish exploratory behavior. Blaser, Rachel; Rosemberg, Denis; Braga, Marcos.
73. Adult zebrafish and conditioned place preference as a model of drug reward. Collier, Adam; Lodinger, Natalie; Khan, Kanza; Caramillo, Erika; Echevarria, David.
74. THC decreases cognitive effort without impairing attentional processes: The role of the cannabinoid system in a distinct form of cost/benefit decision-making. Silveira, M.M; Adams, W.K; Winstanley, CA.
75. Baseline poor-decision making on a rat gambling task is exacerbated following cocaine self-administration and incubation of craving: Investigating individual vulnerability to addiction. Ferland, Jacqueline-Marie N.; Winstanley, Catharine A.
76. Injections of DHβE into the anterior nucleus accumbens or the ventral tegmental area reduce nicotine-induced enhancement of responding for a conditioned reinforcer. Tabbara, Rayane I; Fletcher, Paul J.
77. Sex and age differences in alcohol drinking behavior in socialized vs isolated C57BL/6J mice. Evans, Orion; Currie, Paul; Pastor, Raul.
78. Voluntary consumption of a sweetened alcohol solution is increased by adolescent social isolation via an altered circadian drinking phenotype. Panksepp, Jules; Ryabinin, Andrey.
79. Characterizing responses to a de novo alcohol-associated cue in healthy social drinkers. Mayo, Leah M; de Wit, Harriet.

80. Enhanced sensitivity to cocaine increases perineuronal net staining in the adult medial prefrontal cortex. Slaker, Megan; Sorg, Barbara A.
81. The role of endogenous nociceptin in anxiety-like behaviors in C57/BL6 mice. Perez, Sidney; Marquez, Paul; Hamid, Abdul; Lutfy, Kabirullah.
82. Neurochemical and behavioral comparison of contingent and non-contingent methamphetamine exposure using binge and long-access yoked self-administration paradigms. Keck, Thomas M.; Schweppe, Catherine; Burzynski, Caitlin; Ladenheim, Bruce; Cadet, Jean Lud; Gardner, Eliot L.; Xi, Zheng-Xiong Xi; van Praag, Henriette; Newman, Amy H.
83. Viral-mediated overexpression of miR-495 in the nucleus accumbens shell reduces addiction-related gene expression and motivation for cocaine. Bastle, Ryan; Pentkowski, Nathan; Chaudhury, Trisha; St. Peter, Madeleine; Smith, Colton; Galles, Nicholas; Leslie, Kenneth; Oliver, Robert; Gardiner, Amy; Perrone-Bizzozero, Nora; Neisewander, Janet.
84. Adolescent High Fat Feeding Disrupts Cognitive Flexibility via Downregulation of Reelin in the Prefrontal Cortex (PFC). Labouesse, Marie; Richetto, Juliet; Pujadas, Lluís; Weber-Stadlbauer, Ulrike; Soriano, Eduardo; Langhans, Wolfgang; Meyer, Urs.
85. Exploring the Role of Parasitic Tyrosine Hydroxylase in Toxoplasma Behavior Alteration. Ross McFarland, Zi Teng Weng, David Sibley, Robert Yolken, Mikhail Pletnikov.
86. Sodium butyrate increases contextual fear expression in sign- but not goal-trackers. Fitzpatrick, Christopher J.; Wood, Marcelo A.; Morrow, Jonathan D.

Saturday, June 6

8:00-10:00 **Sensory processing in autism – from the clinic to animal models.** Chair: **Susanne Schmid.** *Oak Bay Rooms*

8:00 Basic information processing deficits in autistic children. Oranje, Bob; Falcher Madsen, Gitte; Vlaskamp, Chantal; Jepsen, Jens Richardt; Durston, Sarah; Cantio, Cathrione; Glenthøj, Birte; Bilenberg, Niels.

8:30 Auditory hypersensitivity in Fragile X Syndrome. Razak, Khaleel; Wen, Teresa; Lovelace, Jonathan; Reinhard, Sarah; Hsu, Mike; Binder, Devin; Ethell, Iryna.

9:00 Sensory filtering and cognitive function in a rat model for autism. DeSilva, Theshani; Schmid, Susanne.

9:30 Preclinical assessment of In vivo electrophysiological phenotypes related to autism spectrum disorders. Siegel, Steven, Gandal, Michael, Billingslea, Eddie.

8:00-10:00 **The mechanisms of stress resilience and safety: Implications for stress-related neuropsychiatric disease.** Chair: **Matthew W. Hale.** *Lecture Theatre*

8:00 Prefrontal control of resilience to adverse events. Baratta, Michael.

8:30 Insular contributions to stress and fear reduction by safety signals. Christianson, John.

9:00 Amygdalocortical circuitry contributes to discriminative reward, fear and safety learning. Sangha, Susan.

9:30 An immunization strategy for prevention of stress-related neuropsychiatric disease. Lowry, Christopher.

10:30 **Presidential Lecture. Stephen Kent**, La Trobe University, Melbourne, Australia. Should we all eat less? Behavioural, endocrine, and immunological consequences of calorie restriction. *Lecture Theatre*

1:00-3:00 **Modulation of memories and flexibility in reward-related learning: From circuits to boutons in the rodent prefrontal cortex.** Chair: **Susan L. Andersen.** *Lecture Theatre*

1:00 Role of the rat medial prefrontal cortex in decisions involving effort, reward, and contingency. Euston, David.

1:30 Prefrontal GABA regulation of cognitive and emotional functions and its relevance to schizophrenia. Floresco, Stan B.

2:00 The role of dopamine D1 and noradrenergic Alpha2A receptors on the development of working memory. Andersen, Susan.

2:30 Structural plasticity of orbital frontal cortex axons during rule learning. Wilbrecht, Linda; Johnson, Carolyn; Peckler, Hannah, Tai, Lung-Hao.

1:00-3:00 **Neuromodulatory control of arousal and motivation by ascending peptidergic systems.** Chair: **Andrew L. Gundlach.** *Oak Bay Rooms*

1:00 Neuromodulatory control of arousal and motivation by ascending peptidergic systems. Gundlach Andrew L.

1:30 The role of relaxin-3 in food intake regulation: Diet and sex-specific aspects. Timofeeva, Elena; Calvez, Juliane; Lenglos, Christophe; De Avila Dal'Bo, Camila.

2:00 Relaxin-3/RXFP3 signalling promotes motivational drive and stress resilience in mice. Smith, Craig; Hosken, Ihaia; Walker, Andrew; Chua, Berenice; Zhang, Cary; Denton, Derek; McKinley, Michael; Lawrence, Andrew; Timofeeva, Elena; Gundlach, Andrew.

2:30 Relaxin-3/RXFP3 networks in food intake and stress responses - neural mechanisms underlying behavioural effects. Blasiak, Anna; Kania, Alan; Lewandowski, Marian H.; Gundlach, Andrew L.

3:30-6:00 **Behavioral Neuroscience through the eyes of those Bob Blanchard influenced.** Chairs: **Brandon L. Pearson; Cliff Summers.** *Lecture Theatre*

3:30 The Blanchard Rules: Bob, from A to Z. Blanchard, D.C.

4:00 The good and the bad: Social influences on drug abuse. Pentkowski, N.

4:20 Channeling Bob Blanchard: Social behavior assays for mouse models of autism. Crawley, J.

4:40 Restraint stress and social defeat: What they have in common. Motta, S.C.; Canteras, N.S.

5:00 Of mice, men, and Bob Blanchard. Eilam, D.

5:20 Events, dear boy, events. Rodgers, R.J.

6:00-7:00 **IBNS Business Meeting** – all members are requested to attend. *Lecture Theatre*

7:30-12:00 **Awards Ceremony and Banquet.** Join us for an evening of networking, music and dancing. Theme: Prince or Pauper…Prizes will be awarded for the 'Best Dressed' and the 'Worst dressed'. *Carson Hall, 2nd Level*

ABSTRACTS

Wednesday, June 3

8:00-10:00 **Symposium**: **Decision-making in animal models for neuropsychiatric disorders.**
Chairs: **Kiyofumi Yamada, Wen-Sung Lai.**

From reward prediction error to dopamine hypothesis of psychosis: Insights from Akt1 mutant mice and schizophrenic patients. Wen-Sung Lai [1, 2, 3], Ching-Chen [1], Hung-Hsiang Liu [1], Ya-Wen Liu [1], Chia-Tzu Li [1], Yao-Chu Chen [1], Chih-Ming Liu [4], Yung-Fong Hsu [1, 2, 3]. [1] Department of Psychology, National Taiwan University, Taipei, Taiwan. [2] Graduate Institute of Brain and Mind Sciences, National Taiwan University, Taiwan. [3] Neurobiology and Cognitive Science Center, National Taiwan University, Taiwan. [4] Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan. Making appropriate decisions involves the ability to update information of alternatives from previous experiences. In particular, the updated reward prediction error (RPE), a discrepancy between the predicted and actual rewards, is regarded as being encoded by dopamine (DA) neurons. Abnormalities in the DA system (or the DA hypothesis) have long been implicated in the explanatory context of schizophrenia (SZ). Specifically, dysregulation of DA systems could alter the appraisal of stimuli through a process of aberrant salience and eventually lead to psychosis. Thus the assessment of RPE could provide a potential behavioral index for dopaminergic activity in the brain that allows for the evaluation of psychosis. Taking advantage of rewarding tasks and model-fitting approach, we tackled this issue in both mutant mice and SZ patients. In the mouse studies, given the involvement of AKT1 (PKB alpha) in the pathogenesis of SZ and the importance of AKT1 in the DA downstream signaling cascade, male Akt1 mutant mice and their wild-type (WT) littermate controls were used to examine the role of Akt1 in the regulation of DA sensitivity, motivational salience, and reward-based choices. In a series of behavioral tasks, we found that (1) Akt1-/- mutant mice reveal a sex- and region-specific effect in the regulation of DA-dependent behaviors and methamphetamine sensitivity; (2) Akt1+/- mutant mice (HET) attributed motivational salience to the lever-CS after Pavlovian-conditioned pairing as WT but they learned the 2-choice dynamic foraging task faster than WT; (3) HET displayed a relatively efficient method of updating reward information from the environment during the acquisition phase of the two natural reward tasks and the reverse section of the dynamic foraging task. Our model-fitting results further revealed that HET update their reward values more rapidly and have more exploratory decisions than WT. These results indicate that Akt1 deficiency modulates natural reward learning and RPE. In the human study, adopted from our mouse task, we developed a dynamic reward task using a card-choosing scenario. SZ patients with low and high psychosis and healthy controls were recruited to perform this feedback-based task to receive money as rewards. Interestingly, our model-fitting results revealed that both psychosis groups show higher learning rates and more exploratory decisions as we reported previously in Akt1 mutant mice. We also found that the degree of exploration increases with the severity of the psychotic symptoms obtained from the PANSS subscores. Collectively, our studies demonstrated an avenue to investigate RPE in both mutant mice and SZ patients and provided a potential link from a genetic deficiency, to neurobiological abnormalities, to higher cognitive functions. Further studies on the emotional regulation of RPE and its related brain activities are in progress. *Keywords:* reward-based decision making, reward prediction error, Akt1 mutant mice, dopamine hypothesis of psychosis, schizophrenic patients, learning rate, perseveration, methamphetamine, striatum. Grant support: Grant numbers 102-2420-H-002-008-MY2 & 102-2628-H-002-003-MY3 from the Ministry of Science and Technology in Taiwan, NTU Hospital grants 102-053 and 104-034, and grants of Drunken Moon Lake Integrated Scientific Research Platform and Aim for Top University Project from NTU.

The insular GABAergic system controls decision-making in healthy and drug-dependent animals. Hiroyuki Mizoguchi [1] and Kiyofumi Yamada [2, 1] Futuristic Environmental Simulation Center, Research Institute of Environmental Medicine, Nagoya University, Nagoya 464-8601, Japan. [2,] Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan. Patients suffering from neuropsychiatric disorders such as substance-related and addictive disorders have impairments in decision-making, which may be associated with their behavioral abnormalities. However, the neuronal mechanisms underlying such impairments are largely unknown. Using a gambling test, we demonstrated that methamphetamine (METH)-treated rats chose a high-risk/high-reward option more frequently, and assigned higher value to high returns, than control rats, suggesting that decision-making was impaired in the drug-dependent animals. Immunohistochemical analysis following the gambling test revealed aberrant activation of the insular cortex (INS) and nucleus accumbens in METH-treated animals. Pharmacological studies, together with *in vivo* microdialysis, showed that the insular neural system played a crucial role in decision-making. Moreover, manipulation of INS activation using DREADD technology resulted in alterations to decision-making. Our findings suggest that the INS is a critical region involved in decision-making, and that insular neural dysfunction results in risk-taking behaviors associated with poor decision-making. Acknowledgements: This work was supported by the following funding sources: Grants-in-Aid for Scientific Research (24111518, 25116515, 25460094, 26120713) from MEXT; “Integrated Research on Neuropsychiatric Disorders” and “Bioinformatics for Brain Sciences,” carried out under the SRPBS from MEXT; a Grant-in-Aid for Health Science Research from the Ministry of Health, Labour and Welfare of Japan; a grant from the Smoking Research Foundation, Japan; a grant from the Uehara Memorial Foundation; a grant from the Takeda Science Foundation; and the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO).

Inhibitory control in young and aged rats and its gating by basal forebrain neuronal inhibition. Jeffrey D. Mayse[1,2], Geoffrey M. Nelson[2], Irene Avila[2], Michela Gallagher[1], Shih-Chieh Lin[2. 1] Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD, USA. [2] Neural Circuits and Cognition Unit, Laboratory of Behavioral Neuroscience, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA. Cognitive inhibitory control, the ability to rapidly suppress responses inappropriate for the context, is essential for flexible and adaptive behavior. While most studies on inhibitory control have focused on the fronto-basal-ganglia circuit, here we explore a novel hypothesis and show that rapid behavioral stopping is enabled by neuronal inhibition in the basal forebrain (BF). In rats performing the stop signal task, noncholinergic BF neurons with phasic bursting responses to the go signal were inhibited nearly completely by the stop signal. The onset of BF neuronal inhibition was tightly coupled with and temporally preceded the latency to stop, the stop signal reaction time (SSRT). Artificial inhibition of BF activity in the absence of the stop signal was sufficient to reproduce rapid behavioral stopping. These results reveal a novel subcortical mechanism of rapid inhibitory control by the BF, which provides bidirectional control over the speed of response generation and inhibition. These results also raise the possibility that age-related impairment in inhibitory control, manifested as increased SSRT, may result from functional impairment of noncholinergic BF neurons. This research is funded by the Intramural Research Program of the National Institute on Aging (NIH, USA) to S.L., NIH P01 AG09973 to M.G. and NIH F31 AG045039 to J.D.M.

The role of Orbitofrontal circuit in supporting learning driven by errors in reward prediction. Yuji Takahashi[1], Geoffrey Schonebaum[1]. [1]National Institute on Drug Abuse Intramural Research Program. Midbrain dopamine neurons have been shown repeatedly to signal errors in reward prediction. Signaling of reward prediction errors requires information about the expected reward and actual reward. Both the orbitofrontal cortex and ventral striatum have been proposed to be the candidate brain regions to provide information about the expected reward to midbrain dopamine neurons. To examine the contribution of the orbitofrontal cortex and ventral striatum to error signaling in midbrain dopamine neurons, we recorded from putative dopamine neurons in ventral tegmental area in rats with neurotoxic lesions of ipsilateral orbitofrontal cortex or ipsilateral ventral striatum. Recordings were made in a simple odor-guided choice task in which different odor cues indicate that a sucrose reward was available in one of two nearby fluid

wells. During recording sessions, we independently manipulated the timing of reward delivery or size of reward across blocks of trials to induce both positive and negative reward prediction errors. Consistent with our prior work in this task, putative dopamine neurons recorded from sham-lesioned rats exhibited robust error signals. Firing of putative dopamine neurons in sham-lesioned rats was greater for an unexpected reward and this activity declined with learning. After learning, the same neurons also showed phasic activity to the reward-predictive cues that differed according to their value, and suppressed firing upon omission of an expected reward. Although both ipsilateral orbitofrontal lesions and ipsilateral ventral striatal lesions did not affect rats' performance on the task and also did not change phasic firing of putative dopamine neurons to reward, putative dopamine neurons recorded in the ipsilateral orbitofrontal- and ventral striatal-lesioned rats failed to show this pattern. Putative dopamine neurons in ipsilateral orbitofrontal lesioned rats still showed phasic increase in firing to an unexpected reward, however this activity was weaker compared to putative dopamine neurons in sham-lesioned rats and failed to reduce firing to reward with learning. After learning, these neurons also failed to suppress firing on reward omission. On the other hands, putative dopamine neurons in ipsilateral ventral striatal lesioned rats fired strongly to an unexpected reward, however this activity diminished rapidly. In addition, these neurons did not show suppression of firing upon an omission of expected reward after learning. These results are consistent with the proposal that inputs from the orbitofrontal cortex and ventral striatum are important sources of the predicitons that midbrain dopamine neurons use to calculate reward prediction errors.

8:00-10:00 **Molecular mechanisms of cocaine-induced cellular and behavioral plasticity.**
Chairs: **David Dietz, Mary Kay Lobo.**

Cocaine-induced transcriptional regulation of mitochondrial biogenesis in nucleus accumbens neuronal subtypes. Ramesh Chandra[1], T. Chase Francis[1], Prasad Konkalmatt[2], Michel Engeln[1], Leah Jensen[1], Amy M. Gancarz[3], Sam A. Golden[4], Gustavo Turecki[5], Scott J. Russo[4], David M.Dietz[3], and Mary Kay Lobo[1] [1]Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD, USA. [2]Department of Medicine, Division of Nephrology University of Maryland School of Medicine Baltimore, MD, USA. [3]Department of Pharmacology and Toxicology, The Research Institution Addictions, State University of New York at Buffalo, Buffalo, NY, USA. [4]Fishberg Department of Neuroscience and Friedman Brain Institute, Graduate School of Biomedical Sciences at the Icahn School of Medicine at Mount Sinai, New York, New York, USA. [5]McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montréal, Québec, Canada. Altered brain energy homeostasis is a hallmark adaptation occurring in the cocaine-addicted brain. Transcriptional regulation of mitochondrial biogenesis (MB), a fundamental component of energy homeostasis, has not been studied in cocaine abuse. We examined ribosome-associated mRNA for MB genes in nucleus accumbens (NAc) medium spiny neuron (MSN) subtypes, those enriched in dopamine D1 vs. D2 receptors, after repeated cocaine (7 days, 20mg/kg). We found that MB ribosome-associated mRNAs are upregulated in D1-MSNs but decreased in D2-MSNs after repeated cocaine. In parallel we found that MB mRNAs are increased in NAc of rodents that self-administer cocaine (10 days, 1mg/kg/infusion) and in postmortem NAc from human cocaine abusers. We then examined transcriptional regulation of MB genes by early growth response 3 (Egr3) using chromatin immunoprecipitation (ChIP) after repeated cocaine. We found that Egr3 is enriched on promoters of MB genes after repeated cocaine and Egr3 ribosome-associated mRNA is increased in D1-MSNs but reduced in D2-MSNs. Next, we genetically manipulated Egr3 in D1-MSNs vs. D2-MSNs during cocaine conditioned place preference (CPP) and cocaine-induced locomotion using viral mediated overexpression or miRNA. Overexpression of Egr3 in D1-MSNs enhanced cocaine CPP and cocaine-induced locomotion, while overexpression in D2-MSNs reduced these behaviors. miRNA knockdown of Egr3 in MSN subtypes produced opposite behavioral responses to those observed with overexpression. Additionally, Egr3 overexpression in D1-MSNs enhanced MB genes in the NAc. Our study establishes a direct role for altered transcriptional regulation of MB in D1-MSNs through Egr3, in cocaine abuse.

A novel role for TGF-β signaling in cocaine abuse. Gancarz-Kausch, A.M.[1] , Schroeder, G.L.[1], Humby, M.S.[1], Mueller, L., Caccamise, A.[1], Neve, R.L.[2], and Dietz, D. M.[1] [1] Department of Pharmacology and

Toxicology; Research Institute on Addiction; Program in Neuroscience, State University of New York at Buffalo, Buffalo NY. [4] Massachusetts Institute of Technology, Cambridge MA. The addicted phenotype is characterized by a long-lasting, chronic, relapsing disorder that persists despite long periods of abstinence, suggesting that the underlying molecular changes are stable and enduring. Many of the long-term effects of cocaine have been shown to be dependent on alterations in gene expression that lead to prolonged adaptations, such as structural changes of medium spiny neurons in the reward circuitry of the brain. We have previously shown that withdrawal from cocaine self-administration (but not non-contingent exposure to cocaine) activates TGF-Beta superfamily signaling in the nucleus accumbens (NAc). Here, we investigate Activin receptor-mediated signaling via downstream Smad3 protein following withdrawal from cocaine self-administration. The Activin type II receptor was increased in the NAc at both the mRNA and protein levels following 7 days of withdrawal from cocaine self-administration. Direct pharmacologic antagonism of the Activin receptor in the NAc resulted in decreased self-administration and attenuated drug-induced reinstatement/relapse behaviors without affecting locomotor activity or food-maintained responding. Pharmacologic activation of the Activin receptor via microinjections of Activin A into the NAc potentiated cocaine-primed reinstatement, without affecting locomotor activity. Withdrawal from cocaine self-administration also increased the expression of phosphorylated-Smad3, the downstream intracellular mediator of Activin signaling. Using viral-mediated gene transfer, we found that overexpression of Smad3 in the NAc potentiated cocaine-primed reinstatement. Importantly, blockade of Smad3 signaling via overexpression of a dominant negative Smad3 (dn-Smad3) attenuated cocaine self-administration. Taken together, these data indicate that Activin/Smad3 signaling is induced following withdrawal from cocaine self-administration and such regulation may be a key molecular mechanism underlying behavioral plasticity. Our ongoing studies are focused on examining how these molecular pathways regulate downstream transcriptional events and structural plasticity following withdrawal from self-administration. This work was supported by grants from NIDA DA037257 and from NIAAA AA007583-11.

Emerging roles for neuron-astrocyte interactions in the neuropathology of cocaine abuse. Kathryn J. Reissner[1.] Department of Psychology, UNC Chapel Hill. Numerous studies have reported a long-lasting reduction in glutamate transporter expression and function in the nucleus accumbens following chronic exposure to drugs including cocaine, nicotine, heroin, and alcohol. Moreover, multiple pharmacotherapeutic drugs which restore expression and activity of the predominant glutamate transporter GLT-1 also impair behavioral measures of drug seeking in preclinical animal models of cocaine addiction. These findings suggest the hypothesis that GLT-modulating drugs may represent a candidate treatment regimen for cocaine addiction. Indeed, at least two drugs which suppress reinstatement to cocaine (N-acetylcysteine and propentofylline) do so in a GLT-1-dependent manner. Further, because GLT-1 expression is restricted to astrocytes in the nucleus accumbens, these findings also suggest that cocaine may mediate important adaptations in astrocyte physiology. In order to test this hypothesis, cells in the nucleus accumbens were transduced with an AAV expressing a membrane-tagged GFP under the control of a GFAP promoter (Lck-GFAP). Following self-administration and withdrawal from either cocaine or saline, slices from nucleus accumbens were immunostained for the presynaptic marker Synapsin I, to allow for concomitant visualization of labeled astrocytes with synapses. Astrocytes in the nucleus accumbens were significantly reduced in size following a cocaine versus saline history, and showed reduced colocalization with synaptic marker Synapsin I. We also found a significant reduction in the expression of glial fibrillary acidic protein (GFAP) in the nucleus accumbens following cocaine versus saline experience. Because astrocytes can exert an important modulatory influence over synaptic and neuronal information processing, ongoing experiments are directed toward understanding (i) the mechanism(s) by which cocaine exerts a hypotrophic effect on accumbens astrocytes, and (ii) the relationship between GLT-1 expression, astrocyte physiology and synaptic colocalization, and drug seeking behaviors. This work is supported by NIH grant DA031790 (KJR).

Cocaine-induced neuroplasticity: at the crossroads of addiction and psychiatry. Mikhail Pletnikov**.** Johns Hopkins University School of Medicine. We propose that evaluating contributions of psychiatric genetic risk factors to drug-induced neuroadaptation not only advances our knowledge of the molecular pathology of addiction, but also bridges research efforts in substance abuse and other psychiatric

diseases that are often co-morbid and likely share common molecular substrates. We found that expression of mutant Disrupted-In-Schizophrenia 1 (DISC1), a product of the Scottish translocation attenuated methamphetamine- and cocaine-induced behavioral sensitization, conditioned place preference and phosphorylation of GSK-3β in the nucleus accumbens (NAc). Notably, the changes in expression of endogenous DISC1 in the NAc and prefrontal cortex were observed following chronic cocaine treatments, supporting the potential role for DISC1 in long-term drug-induced neuroadaptation. In addition, our preliminary studies demonstrated that knockdown of DISC1 expression in the NAc significantly enhanced cocaine-induced activity in mice. Our findings suggest that DISC1 may be involved in the molecular mechanisms of co-morbidity of drug abuse and psychiatric disorders by binding to and inhibiting GSK-3β activity in medium spine neurons of the NAc and pyramidal neurons of the prelimbic cortex.

10:30-11:30 **Keynote: George F. Koob**, NIAAA, NIH, Rockville, MD, USA. The neurobiology of emotions: Insights from the neurobiology of addiction.

The Neurobiology of Emotions: Insights from the Neurobiology of Addiction. George F. Koob, Ph. D. Director, National Institute on Alcohol Abuse and Alcoholism, Washington DC. USA. Emotions can be described in terms of "feeling" states and reflected in classic physiological emotive responses that are interpreted based on the history of the organism and the context. Drugs of abuse elicit powerful emotions that can be interwoven conceptually into this framework. Such emotions range from pronounced euphoria to a devastating negative emotional state that in the extreme can create a break with homeostasis. This allostatic hedonic state has been considered key to the etiology and maintenance of the pathophysiology of addiction. Drug addiction can be defined as the compulsive use of drugs with loss of control over intake that follows a three-stage cycle—*binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*— and that involves allostatic changes in the brain reward and stress systems driven by opponent processes. Functional changes include not only decreases in incentive salience system activity in the ventral striatum (within-system opponent processes) but also recruitment of the brain stress system activity mediated by corticotropin-releasing factor, dynorphin-κ opioid systems, and norepinephrine, vasopressin, hypocretin, and substance P in the extended amygdala (between-system opponent processes). Neuropeptide Y, nociceptin and endocannabinoids, may act as stress buffers also through interactions with the extended amygdala. The thesis argued here is that the brain has specific neurochemical neurocircuitry that encodes the hedonic extremes of pleasant and unpleasant emotions that have been identified through the study of opponent processes in the domain of addiction. These neurochemical systems need to be considered in the context of the framework that emotions involve the specific brain regions now identified as differentially interpreting emotive physiological expression.

1:00-3:00 Travel Award Blitz. Chairs: Kim Gerecke; Jill Silverman

Fluoxetine exposure during adolescence disrupts spatial memory performance in adulthood. Jason B. Alipio, Bryan Cruz, Kristi L. Shawhan, Lace M. Riggs, & Sergio D. Iñiguez**.** Department of Psychology, California State University, San Bernardino, CA 92407**.** Epidemiological reports indicate that mood-related disorders are common in children and adolescents. The prevalence of adolescent depression has resulted in parallel increases in the prescription of fluoxetine (FLX, Prozac), the only antidepressant currently approved by the FDA for treatment within this population. Although treatment can last for years, very little is known about the long-term consequences of antidepressant exposure during early developmental periods prior to adulthood on memory performance later in life. Thus, we exposed adolescent (postnatal day [PD]-35) and adult (PD65) male c57BL/6 mice to FLX (0 or 20 mg/kg) for 15 consecutive days. We then assessed animals' behavioral performance on the Morris Water Maze spatial memory task, three weeks after antidepressant exposure. Specifically, mice were trained to find the location of a submerged escape platform on a single day task of 8 training trials, and memory for the platform location was re-tested after a 24 hour delay (distance traveled and velocity). To increase the demands of the spatial task, the mice returned to the spatial task, 48 hours after training, and completed

a probe trial (escape platform absent), and the total time spent in the quadrant of the target platform location was recorded. We found that FLX exposure, regardless of age, did not influence spatial memory acquisition on the training day. In addition, no differences between the groups were observed when spatial memory was examined 24 hours after training. On the other hand, mice exposed to FLX during adolescence, but not adulthood, spent significantly less time in the target quadrant when tested 48 hours after training (probe trial). Together, our results suggest that as the demands of the spatial memory task increase, spatial memory deficiencies become apparent in adult mice exposed to FLX during adolescence. This highlights the need to further investigate enduring consequences associated with adolescent exposure to FLX treatment.

Interplay between glutamatergic and cannabinoid systems within the dorsal periaqueductal gray matter modulates fear memory encoding and defensive behavior expression in an olfactory conditioning paradigm. Back, F.P.[1]; Carobrez, A.P.[1]. [1]Departamento de Farmacologia, CCB, Universidade Federal de Santa Catarina. 88048900 – Florianópolis, SC, Brazil. Classical conditioning paradigms offer controllable measurements for acquisition/encoding and expression of defensive coping strategies related to traumatic memories. In rodents, microinjections of N-Methyl-D-Aspartate (NMDA) into the dorsolateral portion of the periaqueductal gray matter (dlPAG) elicited defensive behavior (DB) as well as ascending negative valence instruction, serving as unconditioned stimulus (US), which supports fear encoding in conditioning paradigm. Since endocannabinoids are released on demand after neuron depolarization, and anandamide inhibits anxiety-like responses by activating type 1 (CB1) receptors within dlPAG, we proposed to investigate if CB1 receptors blockage would interfere with the CS-US association elicited from dlPAG NMDA activation. Wistar rats implanted with guide cannulas aimed at dlPAG were used throughout the experiments. The olfactory fear conditioning (OFC) protocol was performed during 5 consecutive days and composed of two stages: 1) conditioning (two days; Box A); and 2) expression (three days; Box B). In Experiment 1, twenty four hours after being familiarized in Box A, rats received microinjections (0.2 µl) of NMDA (25-50-100 pmol) and were replaced in the same box now saturated with amylacetate odor (CS). In Experiment 2, rats received microinjections of CB1 receptor antagonist, AM251 (50-100-200 pmol) followed by NMDA (25 pmol) and then were paired with CS. In both cases, OFC expression was performed in a Box B, during three days (familiarization, CS-exposure, Context-only exposure). DB was scored on days 2 (Box A) and 3, 4 and 5 (Box B). Experiment 1 showed that rats receiving 50 or 100 pmol expressed higher levels of DB than those treated with PBS or 25 pmol NMDA during CS association. On the CS exposure, only rats from the 50 and 100 pmol groups were able to show an increased DB. In Experiment 2, the CB1 antagonist AM251 preceded sub effective (25 pmol) NMDA microinjection. CB1 receptor blockage was able to increase DB during the CS exposure when compared to AM251/PBS control. Therefore, the results confirm that NMDA into dlPAG can be used as US in classical conditioning paradigms. In addition, CB1 receptor antagonism potentiated the NMDA sub effective dose, suggesting interplay between glutamatergic and cannabinoid transmission in dlPAG on the modulation of DB. Altogether, the results suggest a dlPAG cannabinoid/glutamatergic balance during the processes of fear memory encoding and expression. Financial Support: CNPq; CAPES and FAPESP.

Baseline poor-decision making on a rat gambling task is exacerbated following cocaine self-administration and incubation of craving: investigating individual vulnerability to addiction. Ferland, Jacqueline-Marie N[1]. & Winstanley, Catharine A[1]. [1]University of British Columbia. Drug addiction is a widespread psychiatric disorder that is defined by a cycle of drug seeking, repeated attempts to quit, and relapse. Maladaptive decision-making is commonly found amongst substance abusers and is thought to play an integral role in the development and maintenance of addiction. Indeed, human studies using the Iowa Gambling Task (IGT), a validated measure of decision-making, have found that substance dependent individuals tend to choose the least advantageous option (associated with less reward over the course of the task) and are less likely to change their strategy following losses compared to controls. These deficits have been found to worsen following withdrawal. Animal studies using self-administration have found that cocaine use impairs a variety of executive functions including reversal learning and impulse control. However, no preclinical work has examined whether cocaine self-administration or prolonged withdrawal has an impact on cost/benefit decision-making. More critically, no animal models

have focused on individual differences in decision-making, which may underlie the likelihood to abuse drugs and relapse. To investigate this relationship, we trained 24 male Long-Evans rats on the Rat Gambling Task (rGT), a rodent analogue of the IGT. In brief, animals were allowed to choose between 4 different nosepoke holes of an operant box, each associated with a different sugar pellet reward (1-4 pellets), penalty time out (5-40s), and probability of receiving a reward over a penalty (0.9-0.4). The advantageous options (those resulting in 1 or 2 sugar pellets) are commonly chosen while the disadvantageous options (3 and 4 sugar pellets) are often avoided. As in the IGT, the goal of the task is to maximize the amount of reward received within a 30-minute session. Once behavioural stability was reached, rats were implanted with jugular vein catheters and were allowed to self-administer cocaine for 10 days followed by 30 days of withdrawal. Decision-making was simultaneously measured by rGT performance throughout the experiment. Results indicated that a subgroup of animals with baseline preferences for the disadvantageous options self-administered greater amounts of cocaine and performed worse (i.e. chose the risky options more) following self-administration. Furthermore, 30 days of withdrawal exacerbated these deficits. These data demonstrate that cocaine self-administration and withdrawal intensifies poor decision-making within a vulnerable subgroup, providing a model by which we can begin to investigate the individual susceptibility to abuse drugs and relapse.

Sodium butyrate increases contextual fear expression in sign- but not goal-trackers. Christopher J. Fitzpatrick[1], Marcelo A. Wood[2], and Jonathan D. Morrow[1,3]**.** [1] Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI 48109, USA; [2] Department of Neurobiology and Behavior, University of California at Irvine, Irvine, CA 92697, USA; [3] Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, USA. Pavlovian conditioned approach behavior has been previously used to identify rats that display enhanced fear expression in response to either cues (sign-trackers; STs) or context (goal-trackers; GTs) following fear conditioning (FC). Levels of histone acetylation in brain regions such as the dorsal hippocampus (dHPC) are critical in consolidating contextual FC and may underlie individual variation in contextual fear expression. Therefore, we hypothesized that low levels of contextual fear expression in STs are a result of decreased acetylation following contextual FC. In Experiment 1, we showed that STs express less contextual fear than GTs following contextual FC, despite equal levels of contextual fear during conditioning. In Experiment 2, we demonstrated that sodium butyrate (200 mg/kg; 10 mL/kg), a histone deacetylase (HDAC) inhibitor, given 1 h prior to contextual FC, enhances contextual fear expression in STs, but not GTs. This is the first demonstration that a HDAC inhibitor given before contextual FC can enhance contextual fear expression in some subjects but not others, and suggests that individual variation in histone acetylation during contextual fear conditioning may underlie individual variation in contextual fear expression. In addition, these results may contribute to a neurobiological explanation of why some individuals but not others develop posttraumatic stress disorder. This work was funded by the University of Michigan Department of Psychiatry (U032826; J.D.M.), the National Institute on Drug Abuse (R01 DA036984; M.A.W.), and the Department of Defense National Defense Science and Engineering Graduate Fellowship (C.J.F.).

Control of the septohippocampal pathway and learning and memory by relaxin-3/RXFP3 neural networks: Viral-based studies in transgenic mice. Haidar M[1,2], Hawkes D[1], Guèvremont G[3], Olucha-Bordonau FE[1,4], Ma S[1,2], Bathgate RAD[1,2], Timofeeva E[3], Smith CM[1,2], Gundlach AL[1,2]**.** [1]The Florey Institute of Neuroscience and Mental Health, [2]Florey Department of Neuroscience and Mental Health, The University of Melbourne, Victoria, Australia, [3]Department of Psychiatry and Neurosciences, Faculty of Medicine, University of Laval, Quebec, Canada, [4]Department of Medicine, Universitat Jaume I, Castellon de la Plana, Spain**.** The 'septohippocampal system' (SHS) is regulated by GABA projection neurons of the brainstem 'nucleus incertus' (NI), including a population that expresses relaxin-3 peptide, which interacts with specific receptors (RXFP3) on neurons in medial septum (MS), hippocampus and other SHS nodes. Local RXFP3 modulation in the MS alters hippocampal ('theta rhythm') activity and spatial memory in rats; via putative actions on GABA and ACh septohippocampal-projection neurons, but similar studies in mice have not been conducted and the nature of RXFP3 effects within the MS/hippocampus are not known. Thus, we are studying relaxin-3/RXFP3 systems in the SHS of relevant transgenic mice. Initial studies of the neurochemical phenotype of topographically distributed RXFP3-positive neurons in

the hippocampus in RXFP3-Cre/YFP 'reporter' mice revealed putative RXFP3-related YFP staining within calretinin-positive neurons in the ventral dentate gyrus hilar region. Secondly, using Cre/LoxP recombination methods, we assessed affective behaviour and working memory in mice with targeted deletion of RXFP3 from the dentate gyrus. In an initial cohort, 'floxed-RXFP3' mice injected bilaterally in the dorsal hippocampal hilar layer with Cre recombinase-expressing adeno-associated virus (AAV1/2-Cre/eGFP) displayed similar locomotor activity, anxiety-like behaviour (light/dark box and elevated plus maze tests), and short-term working memory (Y-maze) to AAV1/2-eGFP-injected control mice (n=8/5, p>0.05). In contrast, this treatment enhanced long-term spatial memory in the Morris water maze, reflected by increased time in the target quadrant during the probe trial; n=8,5 $p<0.05$, unpaired t-test), with no differences in spatial learning detected during acquisition trials (n=8/5, $p>0.05$). The persistence of RXFP3-deleted mice in the target zone may relate to lower behavioural flexibility, whereby mice persist with an 'incorrect solution' rather than modifying their behaviour. Using *in situ* hybridization histochemistry, we are now assessing the overlap of RXFP3 mRNA expression and YFP staining, and changes in RXFP3 mRNA levels in the hippocampi of AAV1/2-Cre/eGFP injected and control mice, as an index of receptor deletion. Further studies are underway to extend these findings, but current data are consistent with the possible regulation of learning and memory retrieval by hilar GABA interneurons and calretinin-positive hilar mossy cells and possible RXFP3 modulation of these networks.

Establishing a role for cortico-thalamic circuitry in cue-driven behaviors. Joshua L. Haight[1], Kurt M. Fraser[1], Huda Akil[1], Susan M. Ferguson[2], and Shelly B. Flagel[1]. [1]University of Michigan, [2]University of Washington. Recently evidence has emerged suggesting the paraventricular nucleus of the thalamus (PVT) is a critical component of the neural circuitry underlying the processing of reward-associated cues, but much of this previous work is confounded by the fact that Pavlovian conditioned reward cues can act as both predictive and incentive stimuli. Here we used a unique animal model to parse the incentive from the predictive properties of reward cues. When rats are exposed to a Pavlovian conditioning paradigm, wherein a discrete cue predicts food reward, two distinct conditioned responses emerge. Some rats, termed sign-trackers (STs), attribute incentive salience to the cue. For others, termed goal-trackers (GTs), the cue serves as a predictive stimulus. We investigated the role of the PVT in the expression and acquisition of these conditioned responses (CRs). First outbred rats were trained in a Pavlovian conditioning task. Following training, ibotenic acid was used to lesion the PVT and the expression of sign- and goal-tracking CRs was measured. When compared to sham controls, PVT lesions attenuated the expression of a goal-tracking response, and increased a sign-tracking response selectively in GTs. Second, we assessed the effects of PVT lesions on the acquisition of sign-and goal-tracking CRs, using selectively bred rats in which it is known a priori whether these rats will acquire a sign- or goal-tracking CR. PVT lesions were performed prior to training and following recovery rats underwent 12 sessions of Pavlovian conditioning. STs with PVT lesions showed an exaggerated sign-tracking response, compared to sham controls of the same phenotype. In addition, PVT lesions attenuated the development of a goal-tracking response in rats with an inherent tendency to goal-track. We are currently following up these studies using more sophisticated techniques to explore which aspects of PVT circuitry are involved in sign- and goal-tracking behaviors. These methods include retrograde tracing from the PVT combined with c-fos immunohistochemistry, as well a novel FLEX-DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technique. These experiments will allow us to parse the role of specific afferent projections to the PVT in the expression of sign- and goal-tracking behaviors. Preliminary results suggest that prelimbic cortical afferents to the PVT are involved in mediating both sign- and goal-tracking behaviors and that "top-down" communication from the prelimbic cortex to the PVT plays a critical role in the attribution of incentive motivational properties to reward cues. Funding Acknowledgments: NIDA F31 DA037680-01A1 (JLH); NIDA T32 DA007821 (JLH).

The evolution of brain structure in dragon lizards. Daniel Hoops[1], Jeremy F. P. Ullmann[2], Andrew L. Janke[2], Marta Vidal-Garcia[1], Timothy Stait-Gardner[3], Yanurita Dwihapsari[3], William S. Price[3], Martin J. Whiting[4] & J. Scott Keogh[1].[1] Evolution, Ecology and Genetics; Research School of Biology; The Australian National University; Acton, ACT, 2601; Australia**.** [2] Center for Advanced Imaging; The University of Queensland; Brisbane, QLD, 4072; Australia**.** [3] Nanoscale Organization and Dynamics Group; School of Science and Health; University of Western Sydney; Penrith, NSW, 2751; Australia**.** [4] Department of Biological Sciences; Discipline of Brain, Behavior and Evolution; Macquarie University; Sydney, NSW, 2109; Australia**.** Many phenotypic traits such as behaviour, body shape, and colour are

shaped by a combination of *both* natural and sexual selection. However, the two evolutionary processes often act in opposition. Natural selection usually acts to improve fitness by increasing survival. In contrast, sexual selection acts to improve fitness by increasing the likelihood of successful mating. This often results in characters, such as conspicuous ornaments and breeding colours, that seem to reduce survival. The interaction between these two modes of selection has been well studied for many traits, but the relative effects of natural and sexual selection on brain evolution is still relatively unknown. How does each type of selection influence brain structure? And how do the relative roles of natural and sexual selection compare to those on other traits closely associated with fitness such as colouration, body size, and key life history traits? To test the interaction between natural and sexual selection, we used high-resolution magnetic resonance imaging combined with traditional histology to document brain structure in 14 lizard species belonging to the Australian genus *Ctenophorus* (known as dragons). These species exist in discrete ecological types or "ecotypes", which are behaviourally distinct, and vary in the strength of sexual selection they experience, which also influences their behaviour. At the level of major brain regions we found only evidence of natural selection acting on brain structure. However, when examining specific brain nuclei that are directly involved with reproductive behaviours we also found evidence that sexual selection has shaped the structure of the brain. We show that both natural and sexual selection have affected the evolution of brain structure.

Neonatal (+)-methamphetamine exposure impairs egocentric learning in the Cincinnati water maze (CWM) and working memory in the radial water maze (RWM) in rats. Sarah A. Jablonski, Arnold Gutierrez, Trisha M. Tee, Kathryn L. Suttling, Michael T. Williams & Charles V. Vorhees. Division of Neurology, Department of Pediatrics, Cincinnati Children's Research Foundation. Rat pups treated with (+)-methamphetamine (MA) on postnatal days (P)6-15 exhibit long-term egocentric route-based learning deficits in the Cincinnati multiple-T water maze (CWM; e.g., Vorhees et al., 2009). Similar impairments in allocentric working memory following developmental MA exposure are not known. Pre-treatment with the spin-trapping agent, N-tert-butyl-α-phenylnitrone (PBN), prevents adult MA-induced dopamine neurotoxicity (Cappon et al., 1996). The objectives of the present experiment were to (1) examine the effects of P6-15 MA (10 mg/kg x 4/day at 2-h intervals) on egocentric and allocentric learning in both young and adult rats and (2) determine whether reactive oxygen species (ROS) generation is a determinant of long-term behavioral deficits induced by MA by pretreating animals with PBN (40 mg/kg). A split-litter design was used with one male/female pair per litter receiving one of four treatments (PBN/MA; Saline/MA; PBN/Saline; Saline/Saline, administered s.c.). Each PBN or saline injection occurred 30-min prior to each MA or saline injection. For behavioral testing beginning on P30 (males), the CWM was truncated and a reduced number of testing days was used, compared with animals tested as adults (females). Regardless of pre-treatment, MA-exposed rats showed a significant increase in CWM errors compared with controls. There was no main effect of PBN or interaction of MA x PBN. As adults, MA-exposed rats showed significant increases in errors and latency to reach the platform compared with controls, however there was no main effect of PBN or interaction of MA x PBN. Rats also underwent the working/reference memory version of radial water maze (RWM). MA-exposed males exhibited a significant increase in reference, working memory, and total errors compared with controls, but there was no effect of PBN or interaction of PBN x MA. MA-exposed females showed a significant increase in reference errors, but there was no effect of PBN or interaction of PBN x MA. Taken together, these findings demonstrate that neonatal treatment with MA induces cognitive impairments that emerge early and affect allocentric working and reference memory and egocentric learning. For the data analyzed so far, the ROS spin-trapping agent PBN was ineffective at attenuating the cognitive deficits induced by early MA exposure. (Supported by T32 ES007051).

Assessing the effects of light dark manipulation and caffeine exposure on zebrafish sleep behavior. Kanza M. Khan[1], Natalie R. Lodinger[1], Adam D. Collier[1], Erika M. Caramillo[1], David J. Echevarria[1]. [1]University of Southern Mississippi. Zebrafish (*Danio rerio*) have been gaining popularity as a model organism in neurobehavioral research over the past several decades. This small teleost fish possess several of the same neurotransmitter and neuropeptides that are found in rodent models and

humans. As such, they provide valuable insight in to the underpinnings of addiction, learning, memory and sleep behaviors. Previous sleep behavior research in zebrafish has focused on individual behavior in response to varying environmental stimuli. In this report we assessed sleep and wake behavior within groups of three fish to alleviate the stress effects of being removed from the shoal. Sleep and wake behavior of the groups were analyzed following three sleep-wake cycle manipulations: (1) constant light conditions, (2) constant dark conditions, and (3) constant light conditions, paired with the administration of an adenosine antagonist (caffeine). Following each sleep-wake cycle manipulation, the cohort of animals was transferred to a separate apparatus for either novel tank dive testing, or for cortisol analysis. We report a decrease in total sleep time following exposure to conditions in which animals were exposed to either constant light, or constant light paired with caffeine administration. Univariate ANOVA revealed a significant difference in the amount of time spent in the top region of the novel tank ($F(2,14)=98.8$, $p<0.001$). Animals in the constant light condition and in the caffeine plus constant light condition exhibited more anxiety like behaviors; exposure to constant dark resulted in a decrease in the number of anxiety-like behaviors produced. Cortisol expression was unchanged in animals exposed to constant light, but was significantly elevated in animals exposed to caffeine and constant light.

The role of hippocampal dopamine D2-type receptors in the social transmission of food preferences in male and female mice. Matta, Richard[1]; Underwood, Emily A.[1]; Leach, Zoe K.[1]; Vertes, Alex C.[1]; Choleris, Elena[1]. [1]Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON N1G 2W1 Canada. The neurotransmitter dopamine (DA) is involved in the regulation of many motivationally relevant behaviors, including drug/alcohol addiction, as well as social interactions, food intake, and social learning. With systemic treatments, our lab has previously implicated DA D1-type receptors in social learning, and DA D2-type receptors in feeding behavior in the social transmission of food preferences (STFP) paradigm in mice (Choleris et al., 2011). However, where these DA receptor families are acting in the brain to influence such behaviors in the STFP remains unknown. The ventral tegmental area has direct dopaminergic projections to many limbic structures, including the nucleus accumbens, amygdala, and the hippocampus—a site important for learning and memory processes, as well as social learning in the STFP. We have previously found that antagonizing dorsal hippocampal DA D1-type receptors blocks social learning in the STFP in both male and female mice (Matta & Choleris, 2014). In an ongoing study, we are microinfusing the DA D2-type receptor antagonist Raclopride (at 10, 14, 18 and 20 µg/µL) directly into the *Cornu Ammonis* 1 (CA1) region of the dorsal hippocampus of adult male and female CD-1 mice. Microinfusions are administered 10 minutes before a 30 minute social interaction, where mice have the opportunity to develop a food preference from a same-sex conspecific. Given the role that mesolimbic DA D2-type receptors play in individually acquired food preferences (e.g. Sclafani et al., 2011), it is hypothesized that hippocampal DA D2-type receptors will also play a role in *socially* acquired food preferences, and *may* also mediate food intake. This study may shed light on the importance that hippocampal DA D2-type receptors contribute to the processing of socially relevant information. Supported by NSERC.

Characterizing responses to a *de novo* alcohol-associated cue in healthy social drinkers. Leah M. Mayo & Harriet de Wit. University of Chicago Department of Psychiatry & Behavioral Neuroscience. It is well-established that drug-related cues can elicit a variety of responses, including enhanced self-reported craving, changes in affect, and a bias in attention, even in the absence of drug. However, little information exists regarding the acquisition of these responses in humans. Previously, we created a novel conditioning paradigm (Mayo et al., 2013) and demonstrated that healthy, non-dependent humans will elicit conditioned responses to a methamphetamine-associated contextual following conditioning (Mayo & de Wit, 2015). Here, we aim to use this same paradigm to determine whether similar conditioning will occur with a different drug: alcohol. Healthy adult social drinkers (N = 36) came into the lab for 6 sessions: a pre-test session, 4 conditioning sessions, and a post-test session. At the pre-test, we assessed baseline responses to two audio-visual study cues. Responses include behavioral preference, emotional reactivity (assessed via facial electromyography of the corrugator and zygomatic muscles) and attentional bias (measured using electrooculography during a modified visual probe task). Participants

then came in for 4 conditioning sessions; 2 each with alcohol (0.6g/kg everclear with either cranberry or orange juice) and placebo (1% everclear solution with juice), administered under double-blind conditions in alternating order. During alcohol sessions, one audio-visual cue was presented on a computer screen for 30min during peak drug effect; the other audio-visual cue was presented during placebo sessions. Following the conditioning sessions, participants completed a post-test session similar to the first session, in which we assessed behavioral preference, emotional reactivity, and attentional bias towards the cues. Following conditioning, participants demonstrated enhanced attention towards the alcohol-paired cue, as indicated by an increase in initial orienting. In addition, subjective responses to alcohol predicted change in attention, such that those who reported "liking" the effects of alcohol more demonstrated a greater increase in initial orienting. This study not only demonstrates *de novo* conditioning in human subjects, but also highlights important differences between conditioning with alcohol and stimulant drugs.

Subtypes of prefrontal cortical NDMA receptors in working memory and normal aging. McQuail, JA[1]; Beas, BS[1]; Simpson, K[1]; Setlow B[2]; Bizon, JL[1]. [1]Dept of Neuroscience, [2]Dept of Psychiatry, University of Florida, Gainesville FL. NMDA receptor (NMDAR)-dependent persistent firing of pyramidal neurons in the prefrontal cortex (PFC) is a likely neurophysiological correlate of working memory. NMDARs are tetramers comprised of an obligate NR1 subunit that variously associates with NR2A or NR2B subunits. These subunits confer unique channel properties as well as differ in relative abundance between PFC pyramidal neurons and interneurons. However, the contribution of specific NMDAR subtypes to working memory and their changes with age are not well understood. To address these questions, the present study combined behavioral analysis of a delayed response (DR) task that is PFC-dependent and sensitive to aging with pharmacological and molecular approaches in young adult (6 months) and aged (22-24 months) F344 rats. Experiment 1 evaluated behavioral consequences of intra-PFC administration of NMDAR antagonists to young adult rats during DR task performance. The NR2B-preferring antagonist Ro-25 6981 produced a significant delay-dependent interaction, impairing accuracy at long delays (>18 s) relative to vehicle. The NR2A-preferring antagonist NVP-AAM077 also significantly impaired accuracy relative to vehicle but there was no interaction with delay. Experiment 2 used Western blotting methods to measure NMDAR subunit levels in PFC homogenates prepared from young adult and aged rats previously tested on the DR task. NR1, NR2A and NR2B subunit expression was lower in aged compared to young and NR2A protein positively correlated with DR accuracy. Apart from marginal reductions in AMPA receptor subunit levels, there were no other age-related changes in synaptic, spinous or dendritic proteins. The present experiments demonstrate that blockade of specific subclasses of NMDAR within the PFC produces significant, but distinct, impairments in performance on a rodent working memory task. Moreover, attenuated expression of PFC NMDARs coincides with onset of age-related working memory deficits and loss of NR2A subunit predicts severity of working memory impairment. Jointly, these studies support a vital role for PFC NMDARs in executive function and further suggest that NMDAR dysfunction may be a causal factor for working memory impairments that are prevalent among older individuals. Ongoing work will determine if positive modulation of NMDARs restores working memory in aged rats and evaluate age-related changes to NMDAR subunit:protein interactions. Supported by AG029421 and McKnight Brain Research Foundation (JLB) and McKnight Brain Institute (JAM).

Assessing the treatment predictive validity of model animals of bipolar mania. Morgane Milienne-Petiot[a,b], Jordy van Enkhuizen[a,b], Mark A. Geyer[a,c], and Jared W. Young[a,c*. a] Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804. [b] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands. [c] Research Service, VA San Diego Healthcare System, San Diego, CA. Bipolar Disorder (BD) is a disabling and life-threatening illness occurring in approximately 1-2% of the population, characterized by fluctuations of mood states from mania to depression. Current treatments for BD have limited efficacy in part due to the fact that all were found serendipitously resulting from limited mechanism-relevant model organisms of BD. BD patients have polymorphisms of the dopamine transporter (DAT), reducing levels in unmedicated patients. Reducing functional DAT levels by pharmacological or genetic means results in a behavioral profile that closely resembles BD mania with

some predictive validity. To date however, neither risperidone (Risp) nor lithium (Li) have been assessed. We therefore examined the efficacy of chronic Li or Risp to remediate the mania-relevant behavior of these model animals. Methods: DAT knockdown (KD) and their wildtype (WT) littermates (2 cohorts) were treated with the antipsychotic Risp (0.03 or 0.3 mg/kg/day; 28 days), or Li (600 mg/L; 10 days). C57BL/6J mice (C57; 2 cohorts) were treated with acute GBR12909 (GBR; 9 or 13 mg/kg) preceded by Risp (0.3 mg/kg/day; 28 days) or Li treatment (1 g/L; 7 days). All animals were then tested in the Behavioral Pattern Monitor (BPM) for 60 min. Results: DAT KD and GBR-treated C57 mice exhibited a behavioral profile consistent with BD mania and as previously reported: Increased transitions, increased specific exploration, and reduced spatial *d*. Risp did not affect the activity of DAT KD or WT mice as measured by transitions [Risp; $F_{(2,38)}$=0.2, p=0.8469; Risp X gene F<1, ns], or specific exploration [F<1, ns]. Similarly, no Risp effect was observed on spatial *d* and no interaction [F<1.2, ns]. Similarly, no effects were observed when Risp was administered to GBR-treated C57 mice [F<1, ns]. In the Li study, the DAT KD mania-relevant profile remained intact irrespective of 600 mg/L Li treatment. In the C57 GBR study however, with 1g/L Li, *post hoc* analyses revealed that Li X GBR treated mice no longer exhibited increased transitions or holepoking (p>0.1), although lower spatial d was still observed (p<0.05) compared to vehicle. Conclusions: Reduced DAT functioning recreated the mania-like exploratory profile in mice. Neither risperidone (28 mg/kg/day) nor lithium (600 mg/L) normalized the mania-like behavior displayed by DAT KD mouse model of BD mania. Risperidone (28 mg/kg/day) also did not attenuate the mania-like behavior of mice treated with GBR12909. In contrast however, a higher dose of lithium (1 g/L) attenuated the effects of GBR12909 on exploration and activity. Serum concentration studies support the need for 1 g/L of lithium to reach concentrations required for the treatment of mania. The DAT KD lithium study will be repeated at this higher dose, while the data presented here partially supports reduced functioning of the DAT as a model organism predictive of treatment effects in mania.

An evaluation of peripheral insulin disruption on behavior, phosphorylated tau levels, and microglia activity. Andrew S. Murtishaw[1], Chelcie F. Heaney[1], Monica M. Bolton[1], Krystal Courtney D. Belmonte[1], Michael M. Langhardt[1], Jefferson W. Kinney[1]. [1]University of Nevada, Las Vegas. Diabetes Mellitus (DM) has been identified as a major risk factor for developing Alzheimer's disease (AD) and vascular dementia (VaD). While DM is a complex metabolic disorder with many associated symptoms and complications, disrupted insulin signaling has been implicated as the aspect most likely making DM a risk factor for dementia-related diseases. Much research has been conducted using streptozotocin (STZ), a compound that targets and destroys insulin producing pancreatic β-cells, to better understand DM. Additionally, the administration of STZ has been used to model sporadic Alzheimer's disease due to its ability to alter behavior and hyperphosphorylated tau in the brain. Much of the DM research utilizing STZ relies on the administration of very high single dose or repeated daily doses of a slightly lower dose, both of which are often associated with an increased mortality rate and renders sick animals not optimal for behavioral testing — particularly sensitive learning and memory tasks. The purpose of this experiment was two fold. First, we set out to create an optimal dose schedule to be administered over the course of several weeks that would lead to a viable and sustainable diabetic state, including the elevation of blood glucose levels, alterations in learning tasks, and dementia-related protein changes, while eliminating the increased mortality rate and maintain physically healthy rodents. Second, microglia activity is not well-documented following peripheral STZ administration; therefore we investigated the effect of peripheral STZ on microglia in several areas of the hippocampus, hypothalamus, and the cortex. We were able to create an optimized multiple low-dose STZ administration schedule, over the course of 15 days, that lead to significantly elevated blood-glucose levels and overall healthy animals following a battery of standardized behavioral tests. Starting the sixth week after the first STZ injection, animals were assessed for learning and memory in the open field and Novel object recognition tasks, following which brains were removed and prepared for either western blotting to investigate tau pathologies in the cortex and hippocampus or for immunohistochemistry to evaluate microglia activity in the cortex, hippocampus, and hypothalamus.

Akt signaling within the nucleus accumbens regulates functional reactivity to chronic social defeat stress in male mice. Eric M. Parise[1], Lyonna F. Alcantara[1], Omar K. Sial[1], Eric J. Nestler[2], and Carlos A. Bolaños-Guzmán[1]. [1]Department of Psychology and Program in Neuroscience, Florida State University, Tallahassee, FL. [2]Mount Sinai School of Medicine, New York, NY. Exposure to stress is a risk factor associated with the development of neuropsychiatric disorders. Unfortunately, the mechanisms that

mediate the differential responses to stress are not well understood. Chronic social defeat stress (CSDS) is an ethologically relevant stress model capable of inducing core symptoms of depression and posttraumatic stress disorder that are measurable in rodents. The mesolimbic dopamine system, which includes the ventral tegmental area (VTA) and its projection regions, namely the nucleus accumbens (NAc), has received attention for its involvement in modulating responses to stress, as the VTA-NAc circuit plays a crucial role in integrating reward- and emotion-related behaviors. Akt signaling within the VTA regulates responses to stress; however, its role within the NAc is unknown. The present study was designed to assess the role of Akt-signaling within the NAc in modulating functional and biochemical responsivity to social defeat stress. Adult male mice were subjected to 10 days of CSDS followed by a social interaction test (SIT) 24 h after the last defeat. Mice were sacrificed either 24 h (short-term) or 1 month (long-term) after the SIT, and their brains were then processed for mRNA and protein changes in the NAc. Socially defeated mice show significant increases in Akt mRNA in both the short- and long-term conditions when compared to non-stressed controls. We observed increased phosphorylation of Akt protein after CSDS, but only in the long-term group, findings consistent with the enduring behavioral deficits observed in the SIT. This data suggests that Akt signaling within the NAc is significantly disrupted after CSDS exposure. To better understand the involvement of Akt in mediating stress-induced behavioral responding, we delivered herpes simplex virus (HSV) vectors overexpressing a constitutively active form of Akt (HSV-Akt_{ca}), a dominant negative inhibitor of Akt (HSV-Akt_{dn}), or GFP (HSV-GFP) into the NAc and assessed functional reactivity to stress. Mice receiving HSV-Akt_{ca} into the NAc and then subjected to a sub-threshold defeat displayed significantly increased social avoidance. Conversely, inhibition of Akt, with HSV-Akt_{dn}, in the NAc was sufficient to reverse the avoidant phenotype induced by 10 days of CSDS. These results suggest that Akt signaling within the NAc plays a crucial role in gating sensitivity to stress and may, in conjunction with changes in the VTA, mediate the depressive-phenotype induced by CSDS.

Regulation of discriminative fear conditioning by prefrontal and striatal subregions. Patrick T. Piantadosi[1], Dylan C.M. Yeates[1], Stan B. Floresco[1]. University of British Columbia. Fear is a highly salient emotion that can control motivated behavior. The neural substrates underlying such behavior have been investigated using Pavlovian fear conditioning, whereby an organism is exposed to a single conditioned stimulus (CS) that becomes predictive of an aversive unconditioned stimulus. Less is known about the circuitry underlying appropriate fear discrimination in the presence of both an aversive conditioned stimulus (CS+) and one that is explicitly neutral (CS-). Here, we used reversible inactivations to examine the contribution of two subregions of the rat medial PFC (mPFC), the prelimbic (PL) and infralimbic (IL) cortex, and two subregions of the nucleus accumbens, the shell (NAcS) and core (NAcC), to the acquisition and expression of discriminative fear conditioning. Male Long Evans rats were trained to lever press for sucrose reward on a variable-interval 60s (VI-60) reinforcement schedule. They were then subjected to discriminative fear conditioning entailing eight, 30s presentations each of a CS+ (9kHz tone and continuous cue light terminating with 0.5mA/0.5s footshock) and a CS- (1kHz tone and flashing house light, no shock). Two days later, rats underwent a test session during which each CS was presented four times during VI-60 lever pressing. A second test session was given on the following day, to examine potential extinction learning during test. To assess the impact of aversive conditioning on motivated behavior, the suppression of lever pressing during each CS served as the index of conditioned fear. Rats received inactivation of either the IL or PL (75ng baclofen/muscimol in 0.33µl saline per side) or NAcS or NAcC (75ng baclofen/muscimol in 0.3µl saline per side) or saline infusion prior to either the conditioning or test phase of the task. Control rats in each condition displayed appropriate discrimination, suppressing lever pressing during the CS+ exclusively. Inactivation prior to conditioning had no affect on the subsequent expression of discriminative fear during the first test day, regardless of the region inactivated. However, IL inactivation prior to conditioning lead to somewhat more rapid extinction of fear on the second test day. Interestingly, inactivation of PL, IL, and NAcS prior to the expression test markedly reduced suppression in response to CS+ presentations, suggesting that these regions contribute to motivational suppression in a fear context. Inactivation of NAcC, however, had no impact on conditioned suppression. These results point to a potential corticostriatal circuit regulating the ability of aversive cues to control ongoing motivated behavior.

A novel task to assess reversal learning in mice in a home-cage environment. E. Remmelink[1,2,3], M. Verhage[2], A.B. Smit[3], M. Loos[1]. *[1]Sylics (Synaptologics B.V.), Amsterdam*. *[2]Department of Functional Genomics, CNCR, VU University, Amsterdam*. *[3]Department of Molecular and Cellular Neurobiology, CNCR, VU University, Amsterdam*. Several neurological and psychiatric disorders are characterized by deficits in cognitive flexibility. Measuring cognitive flexibility in mice enables the investigation of mechanisms underlying these deficits. The majority of currently available behavioral tests targeting this cognitive domain are operant tasks, which require food-deprivation and extended training periods. Here, we describe a novel test for measuring reversal learning in an automated home-cage environment (PhenoTyperTM) that circumvents extended training periods and food-restriction and reduces labor intensive and stress-inducing animal-handling. All behavior was video tracked and hardware actions were triggered by the position of the mouse. After an initial habituation period to the home-cage, a wall with three holes was placed in front of the pellet dispenser spout. For two days, mice had to learn to earn all their food by going through the left hole in the wall (Initial learning). During the subsequent 2 days, the correct and rewarded hole was switched to the right hole (Reversal learning). During this task the dispenser distributed 1 reward for every 5 times the mouse went through the correct hole (FR5 schedule). The number of passages needed to reach a criterion of 24 out of 30 entries through the correct hole, computed as a moving window, was used as a measure of performance during both stages. Perseverative as well as random errors were assessed during the reversal learning stage. The total number of entries through the wall, and the distance moved, were assessed as measures of general activity. Most mice tested were able to attain the performance criterion of 80% correct within 1 day. As expected, mice took significantly longer to attain this performance criterion during the reversal phase. All individuals were able to attain the criterion within the two available reversal learning days. Task activity was predominantly limited to the dark phase, suggesting that task performance had no impact on circadian rhythm. Additionally, we tested mutant mice with known deficits in either initial learning or reversal learning, and were able to replicate those deficits by using our task. To conclude, we have developed a short 4-day protocol for reversal learning, which runs without human intervention. This task provides an efficient way of screening mice for discrimination and reversal learning in a home-cage environment, in which handling is absent and no food-restriction is required.

Individual differences in locomotor activity correlate with behavioral responses to ethanol in zebrafish: Potential roles of the dopaminergic and serotonergic neurotransmitter systems. Steven Tran[1], Magda Nowicki[2], Arrujyan Muraleetharan[2], Diptendu Chatterjee[2], Robert Gerlai[1, 2]**.** [1]Department of Cell and Systems Biology, and [2]Psychology, University of Toronto**.** Zebrafish have been previously shown to exhibit individual differences in baseline locomotor activity (e.g. hyperactive and hypoactive phenotypes) which persists over time and across different experimental contexts. These individual differences in behavioural responses may potentially represent underlying differences in neurotransmitter systems and biochemical pathways. Furthermore, these differences may also alter how individual zebrafish respond to a drug challenge. To examine these questions we quantified baseline locomotor responses and subsequently exposed each zebrafish to either 0 or 1.0% v/v ethanol for 30 minutes. Behavioural measures including total distance traveled (cm – a measure of activity), variance of the distance to bottom (cm^2 – a measure of vertical exploration) and absolute turn angle (deg – a measure of erratic movement) were quantified and averaged over the last 10 minutes of exposure. Immediately following the acute ethanol challenge, zebrafish were euthanized and their brains dissected. The levels of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) were quantified from whole brain tissue using high precision liquid chromatography (HPLC). In addition, we calculated ratios to determine indexes of monoamine metabolism (breakdown) including dopamine turn over (DOPAC:DA) and serotonin turn over (5-HIAA:5-HT). Zebrafish that were initially classified as hyperactive exhibited a behavioural profile indicative of a less anxious phenotype and a neurochemical profile suggesting increased dopamine and serotonin metabolism. Zebrafish initially classified as hypoactive exhibited a behavioral profile indicative of a more anxious phenotype and a neurochemical profile suggesting decreased dopamine and serotonin metabolism. In response to the acute ethanol challenge, there was an overall increase in total distance traveled and a decrease in the levels of DOPAC and 5-HIAA in the brain. Behavioral and neurochemical differences between hyperactive and hypoactive zebrafish were attenuated by acute ethanol exposure. Overall, we identified

significant differences in the dopaminergic and serotonergic neurotransmitter system in zebrafish which appear to correlate well with behavioral measures including locomotor activity and anxiety-like behavioral responses. Acknowledgements: Funding supported by an NSERC Discovery Grant issued to R.G. and an NSERC CGSD issued to S.T.

3:30-4:30 **Neuronal correlates of rodent empathy.** Chairs: **Ksenia Meyza, Ewelina Knapska.**

Modeling vicarious fear in adolescent mice. Jules B. Panksepp[1]. [1] Department of Behavioral Neuroscience, Oregon Health and Science University. This talk will summarize an experimental approach for measuring vicarious fear in laboratory mice. The paradigm entails allowing 'witnesses' to observe 'targets' undergoing a series of tone-shock parings, followed by an assessment of how the witness mice respond to tone-playbacks. Individuals from the gregarious C57BL6/6J (B6) strain exhibit heart rate deceleration in response to conspecific distress and freeze to social distress-associated cues, whereas mice from the less social BALB/cJ strain are much less responsive. This genetic background difference can be reproduced when playback of distress vocalizations is paired with a tone, indicating that the ascending auditory pathway is a major system engaged by conspecific distress. More recent studies demonstrate that the social environment during the first 3 weeks post-weaning are critical for this vicarious freezing phenotype: B6 mice deprived of adolescent social interaction do not maintain a vicarious freezing phenotype 24 hours post-conditioning. A longitudinal study of sociability and tone induced-vicarious freezing in 6 strains demonstrated substantial heritability of both phenotypes, but no genetic relationship between them, suggesting that sociability does not necessarily predict vicarious responding to others' distress. Along with the work of others, our findings bear similarity to the construct of empathy, whereby individuals adopt an emotional state more appropriate to another's situation than one's own. I will conclude with our recent attempts to map metabolic and inducible transcription factor responses in the mouse brain as they experience others' distress. Continued development of an empathy construct in rodents offers unique opportunities to further examine fundamental issues in empathy research, such as the role of mirror neurons and the degree to which positive emotions can be engaged during vicarious experiences.

Affective drivers of helping behavior in rats. Inbal Ben-Ami Bartal**.** Prosocial behavior refers to actions that benefit another individual and is manifested across diverse species, from insects and birds to humans. It is an adaptive behavior that promotes group thriving and survival. Multiple mechanisms have evolved to support prosocial behavior across taxa. In humans, empathy is a powerful driver of prosocial behavior. In the narrow sense, empathy refers to the recognition and sharing of affective states between individuals, and can lead to concern for the welfare of others in need or distress. Empathy is thought to have evolved in the context of parental care, and then expanded to the broader social group. Empathy stems from activity in the brain stem, paralimbic areas and the thalamus, structures linked to affective processing which are highly conserved across mammalian species. Robust evidence exists showing that certain mammals respond to the distress of conspecifics with a congruent affective arousal. For instance, mice will freeze in the presence of a conspecific receiving a foot shock, and show hyperalgesia when witnessing a familiar other in pain. Yet, it is unclear whether this rudimentary form of empathy motivates prosocial behavior in non-humans. The rat Helping Behavior Test shows that rats will learn to release a cagemate trapped inside a restrainer, a demonstration of prosocial behavior. Helping is intentional and selective, and rats will not help strangers of another strain, unless they have had social experience with a member of that strain. In my talk, I will present evidence showing that an affective response in the free rat to the distress of the trapped rat is a primary driver of this helping behavior, suggestive of a common mechanism underlying prosocial behavior in rats and humans.

Neural Mechanisms of Fear Conditioning by Proxy: Social Transmission of Fear in Rats. Marie-H. Monfils**.** Department of Psychology, University of Texas at Austin**.** Most animal models of fear learning focus on creating a CS-US association through direct experience using variations of Pavlovian fear conditioning. We have previously shown that some rats will display a conditioned response (CR; e.g. freezing) to a cue after interacting with a cage-mate previously fear conditioned to a cue while this cage-

mate is displaying the CR during the presentation of a cue (Bruchey et al., 2010). The amount of freezing exhibited by the previously naïve rat, which has now been fear conditioned 'by-proxy', during a test session the following day was positively correlated with the amount of time spent interacting socially with the freezing rat (Bruchey et al., 2010) suggesting that this form of learning is social in nature. In the current study, we sought to further investigate the individual differences seen in social fear acquisition by controlling for dominance status of the rats undergoing this fear conditioning by-proxy (FCbP) paradigm. One rat from each cage of a triad was fear conditioned to a tone CS. The next day, the conditioned rat was returned to the chamber accompanied by a second cage-mate while the tone was played in the absence of the foot-shock (FCbP). Socially acquired fear was measured as freezing displayed by this second cage-mate to the CS alone on the following day. Dominance in male rats was determined using the methods of Pellis et al. (1993) by observing play behavior amongst a triad of related adults. We then manipulated which rat of the hierarchy was directly fear conditioned or fear conditioned by-proxy. Our results show that dominance hierarchy significantly impacts social transmission of fear in rats. Funded by an NIMH R01 research grant to MHM.

Neuronal circuits underlying emotional contagion. Ewelina Knapska, Nencki Institute of Experimental Biology, Warsaw, Poland. In its simplest form empathy can be characterized as the capacity to be affected by and/or to share the emotional state of another being (emotional contagion). An animal can socially learn about potentially harmful stimuli either by observing a conspecific in danger or by interacting with a conspecific, which had experienced danger. These two ways of learning presumably involve different neuronal circuits within the amygdala, a brain structure crucial for fear learning and memory. We have compared activation of the amygdala in two rat models of emotional contagion: observational fear learning (direct danger) and social transfer of emotions (indirect danger). We observed different behaviors (passive vs. exploratory, respectively) in the observer rats and the activation of different neuronal circuits. The central amygdala was specifically activated by interaction with a conspecific, which had experienced danger. To elucidate the role of neuronal circuits in the central amygdala of the observers, we used two methods of functional mapping we have developed recently: a combination of retrograde tracing with c-Fos immunohistochemistry and transgenic rats expressing in behaviorally activated neurons a PSD-95:Venus fusion protein and injected with anterograde tracer. We have identified several brain structures in which neurons receiving projections from the central amygdala are activated during social interaction with emotionally aroused partner. All of them are rich in neurotransmitters involved in modulation of attention and learning. We also identified active projections that originate in both cortical (prelimbic, infralimbic and insular cortices), as well as in subcortical (basolateral amygdala and hippocampus) structures. Moreover, we show that most of the activated cells are GABA-ergic neurons. To test whether the activated circuits are similar for the socially and non-socially induced emotions, we used double immunodetection for a PSD-95:Venus construct and endogenous c-Fos. We show that about 70% of neurons is activated by both social interaction with fear conditioned partner and subsequent fear conditioning. These results suggest that there exists a group of neurons in the central amygdala that is involved in integrating information from external world and internal milieu and modulating function of other brain structures and that part of these cells is specifically involved in socially induced emotions.

3:30-4:30 **From the lab bench to the field: Translational research approaches for investigating mild Traumatic Brain Injury (mTBI).** Chair: **Chand Taneja.**

Evaluating chronic cognitive deficits in rats across a spectrum of TBI severities. Cole Vonder Haar[1]. [1]University of British Columbia. Traumatic brain injury (TBI) is one of the largest problems facing the medical community today. Nearly 1% of the population experiences a TBI every year with 2% of those dying and another 10-15% requiring hospitalization. However, even in those with milder injuries, a significant portion go on to develop debilitating neurodegenerative diseases and severe psychiatric symptoms such as impaired attention and poor impulse control. In order to model psychiatric-like behaviors in rats, complex cognitive tasks are needed. In the following study, rats were trained on the five-choice serial reaction time task, a behavioral measure of sustained attention and motor impulsivity. Rats are trained to respond to a brief light (0.5 s) presented at one of five holes across the visual field and

premature (impulsive) responses to these holes are punished. Once a high level of performance was reached, rats were given a bilateral frontal mild, moderate, severe or sham brain injury procedure via controlled cortical impact. Following a recovery period, rats were re-assessed for over three months on the task. Brain injury resulted in initial deficits across all groups, graded by injury severity, in both attention and impulsivity during the acute phase (< 1 month). Considerable recovery on the attention measure was shown in moderate- and mild-injured animals, however only the mild ever re-obtained sham levels. Impulsivity remained strongly elevated in severe and moderate animals, and mild animals showed a trend towards more impulsive behavior in the chronic phase (> 1 month). Finally, all animals (including severely impaired ones) were able to complete the task when the difficulty was adjusted, demonstrating that performing the task itself is not too difficult for rats post-TBI. Upon examining the brains, the extent of the damage and neuroinflammatory status were found to be significant predictors of behavioral performance. These physiological markers were found to correlate very strongly with the individual variation observed within the brain injury groups. The results observed in this study highlight the need for sensitive behavioral measures of assessment for brain injury, particularly when evaluating milder injuries and the utility of brain-based markers for predicting individual outcomes. Funded by the Canadian Institutes for Health Research.

The effects of multi-trauma on mild TBI outcome. Stuart J McDonald. La Trobe University, Australia. Multi-trauma is an international medical problem and commonly involves concurrent traumatic brain injury (TBI) and peripheral bone fracture. Although many TBI patients suffer concurrent bone fractures, pre-clinical TBI research utilises 'single-hit' models not featuring the pathophysiological complexities likely induced by multi-trauma, which may account for failures in translating pre-clinical findings to the clinical setting. Therefore, here we developed a novel mouse model of multi-trauma, and investigated whether peripheral bone fracture affects mild TBI (mTBI) pathogenesis and outcomes. Male mice were assigned into four groups: sham-mTBI and sham-fracture (sham); sham-mTBI and fracture (FX); mTBI and sham-fracture (mTBI); and mTBI and fracture (MULTI). The injury methods included a weight-drop TBI model and a closed tibial fracture. After the assigned injuries, mice were given either a 24 h or 35 day recovery period. Behavioral testing and *in vivo* MRI were conducted 35 days post-injury, and brain tissue was collected at 24 h and 35 days post-injury for post-mortem analysis. MULTI mice displayed abnormal behaviors in the open field compared to all other groups, had significant motor impairments on the rotarod compared to the sham and mTBI groups, and had enlarged ventricles and diffusion abnormalities in the cortex and hippocampus compared to all other groups. These changes occurred in the presence of heightened neuroinflammation in MULTI mice at 24 h and 35 days post-injury. Together these findings indicate that tibial fracture worsens mTBI outcomes, and that exacerbated neuroinflammation may be an important factor contributing to these effects and warrants further investigation.

Treatments and biomarkers for mild traumatic brain injuries. Shultz, S.R.[1], Wright, D.K.[1], Tan, X.L.[1], O'Brien, T.J.[1]**.** *[1]The Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne***.** Mild traumatic brain injuries (TBI), including concussions, are common worldwide. In light of growing clinical evidence suggesting that mild TBIs may have cumulative and lasting neurological effects, and are associated with neurodegenerative disease, mild TBI is now recognized as a serious medical problem. Unfortunately, little is currently known regarding the factors and pathophysiological mechanisms that contribute to the reduced neurological capacity following mild TBI, nor are there any interventions known to prevent them. Here Dr. Shultz will present findings from studies that have assessed i.) the long-term effects of mild TBI in both rats and retired athletes; ii.) the use of behavioural, MRI, and blood-based biomarkers in the management of mild TBI in rat and human studies; and iii.) the use of novel pharmacological interventions for mild TBI in rodent models.

4:30-5:30 **Basic and translational aspects of drug addiction.** Chair: **Jean Lud Cadet.**

Epigenetic and transcriptional bases of methamphetamine addiction. Jean Lud Cadet, M.D. Molecular Neuropsychiatry Research Branch, NIDA IRP, Baltimore, MD 21224**.** Methamphetamine use disorder is a neuropsychiatric disorder characterized by binge episodes, periods of abstinence, and craving-induced relapses. Humans addicted to methamphetamine experience cognitive impairments that

impact their activities of daily living. Models of methamphetamine abuse in rodents have revealed that animals will readily learn to self-administer methamphetamine. Our microarray studies have shown that methamphetamine taking is associated with transcriptional changes in the striatum measured at various times after cessation of methamphetamine taking. Specifically, there was increased expression of genes that are involved in transcription regulation. These genes include cyclic AMP response element binding (CREB), ETS domain-containing protein (ELK1), and members of the FOS family of transcription factors. The expression of brain-derived neurotrophic factor (BDNF), tyrosine kinase receptor, type 2 (TrkB), and synaptophysin was also increased at that time. Chromatin immunoprecipitation (ChIP) studies showed that methamphetamine-induced transcription was regulated via phosphorylated CREB-dependent mechanisms. In contrast, methamphetamine self-administration was associated with decreased expression of transcription factors including junD. Constituents of chromatin-remodeling complexes were also downregulated after methamphetamine withdrawal. Altogether, our results show that methamphetamine abuse is associated with altered regulation of a diversity of gene networks that impact cellular and synaptic functions. Elucidation of the way that gene products interact to mediate methamphetamine addiction should expedite the development of better pharmacological treatment of methamphetamine addicted patients. Acknowledgements: This research is supported by the NIH/NIDA Intramural Research Program.

Basic and Translational Aspects of Impaired Dopamine Signaling in Methamphetamine-Induced Cognitive Dysfunctions. Kristen A. Keefe[1,2], Melissa Barker-Haliski[1], Elissa Pastuzyn[1], Paul A. Garris[2], Christopher Howard[3]. [1]University of Utah, [2]Illinois State University, [3]Salk Institute for Biological Studies, [4]Eastern Washington University. Cognitive impairment often arises as a consequence of drug abuse and is thought to contribute to the development of addiction and treatment failure. Further, recent data indicate that individuals with a history of methamphetamine (METH) use are more likely to develop Parkinsonism, suggesting that they may experience a prolonged period of pre-clinical DA loss, which may contribute to impaired cognition. Decision making/action selection is a critical component of human cognition, with two processing modes contributing—controlled/goal directed and automatic/habitual. Evidence suggests that plastic processes involving phasic DA signaling, DA D1 receptor activation, and the effector immediate early gene *Arc* in striatonigral efferent neurons contribute to the development of these critical cognitive processes mediated by dorsal striatum. Our previous work has shown that the *Arc* expression, particularly in striatonigral efferent neurons, and phasic DA signaling are disrupted in striata of rats with METH-induced partial DA loss. More recent preliminary data suggest that nuclear export of plasticity-related immediate early gene mRNAs may be differentially regulated in striatonigral vs. striatopallidal efferent neurons. That is, more striatonigral efferent neurons have *zif268* in the cytoplasm, whereas more striatopallidal efferent neurons have *zif268* mRNA restricted to the nucleus. Our recent unpublished data also suggest that we can pharmacologically restore METH-induced deficits in phasic DA signaling with administration of L-Dopa, and that enhancing phasic signaling can reverse deficits in striatal efferent neuron gene expression. Taken together, these findings suggest that impaired phasic DA signaling arising from METH exposure is associated with disrupted subcellular regulation of plasticity-related genes in striatonigral efferent neurons, which may then contribute to METH-induced deficits in cognitive function. Further, our preliminary data suggest a pharmacological approach to restoring these functions.

Molecular mechanisms underlying incubation of methamphetamine craving. Irina N. Krasnova[1], Bruce Ladenheim[1], Michael T. McCoy[1], Yavin Shaham[2], Jean Lud Cadet[1]**.** [1]Molecular Neuropsychiatry Research Branch, Intramural Research Program, NIDA, NIH, DHHS; [2]Behavioral Neuroscience Research Branch, Intramural Research Program, NIDA, NIH, DHHS**.** Treatment of methamphetamine addiction is problematic due to high rate of relapse to drug use after periods of abstinence. However, animal models used to study drug craving and relapse do not incorporate negative consequences of drug use that is a factor promoting abstinence in humans. Here, we studied incubation of methamphetamine craving in rats after suppression of drug seeking by adverse consequences (punishment) and neuroplastic changes associated with relapse. Rats self-administered methamphetamine or palatable food for 9 h/day for 14 days. Subsequently, for one group within each reward type lever-presses were

punished by footshock for 10 days, for the other group lever-presses were not punished. Next, we assessed reward seeking in extinction tests on withdrawal days 2 and 21 and studied related plastic changes in the hippocampus and dorsal striatum using ChIP-Seq, RT-PCR and Western blot. Punishment suppressed methamphetamine or food self-administration. During the relapse tests, punished and unpunished methamphetamine- and food-trained rats showed higher cue-induced reward seeking on withdrawal day 21 vs day 2. We found decreases in the expression of histone diacetylase (HDAC) 5 and HDAC9 in the striatum of punishment-sensitive rats in comparison to punishment-resistant animals. We also found reductions in HDAC9 and HDAC10 in the hippocampus of punishment-sensitive animals. These results show that incubation of methamphetamine craving occurs after punishment-induced suppression of methamphetamine self-administration. Our findings using this model that closely approximates human conditions suggest that HDAC5, HDAC9 and HDAC10 may serve as promising targets for the development of efficient therapy against methamphetamine addiction.

Glutamatergic medications for substance use disorders – are we any closer? M. Foster Olive[1], Lucas W. Watterson[1], and Peter R. Kufahl[1.] Department of Psychology, Arizona State University, Tempe, AZ 85287-1104**.** Several glutamatergic medications have been clinically evaluated for the treatment of methamphetamine (METH) addiction. Thus far, these medications (e.g., gabapentin and topiramate) have demonstrated only marginal clinical effects, and exert their actions via multiple pharmacological targets, one of which being ionotropic glutamate receptors. Yet there is substantial preclinical evidence that ligands acting on metabotropic glutamate receptors (mGluRs) may also be of potential clinical use in the treatment of METH addiction. We have recently tested the ability of the mGluR5 negative allosteric modulator fenobam and the mGluR2/3 agonist LY379268 to attenuate cue- and drug-primed reinstatement of METH seeking in rats. In rats trained to self-administer METH, sucrose, or food under limited access conditions (2 hr/day), fenobam (5, 10, or 15 mg/kg) dose-dependently attenuated cue- and METH-induced reinstatement, but also attenuated cue-induced sucrose and food seeking. In a separate study, rats trained to self-administer METH or sucrose under limited access conditions (ShA, 90 min/day) or METH under extended access conditions (LgA, 6 hr/day), LY379268 (0.3, 1 or 3 mg/kg) dose-dependently attenuated cue-induced METH seeking, with LgA rats demonstrated greater sensitivity to LY379268 than ShA rats, indicating altered mGluR2/3 following extended vs. limited METH access. LY379268 also dose-dependently attenuated METH-primed reinstatement, but with similar dose sensitivity between LgA and ShA rats. LY379268 also dose-dependently attenuated cue-induced reinstatement of sucrose seeking. Together, these findings suggest that clinical trials are warranted to assess the efficacy of pharmacological agents that either activate mGluR2/3 receptors or inactivate mGluR5 receptors in reducing METH craving or relapse. Such ligands are currently in clinical trials for treatment of other neuropsychiatric disorders such as depression, schizophrenia, or Fragile X syndrome. However, the specificity of such ligands for behaviors motivated by METH vs. non-drug reinforcers should also assessed in these trials. Funding provided by NIH grants DA025606.

4:30-5:30 **Brain lipids in neuropsychiatric disorders.** Chairs: **Christian P. Müller, Miriam Schneider.**

Effects of decreased DHA in the adult brain: implications for depression. Levant, Beth. University of Kansas Medical Center, Kansas City, KS, USA. Clinical and epidemiologic studies implicate low dietary and tissue levels of the n-3 polyunsaturated fatty acid docosahexaenoic acid (dha; 22:6n-3) in the etiology of both non-puerperal and postpartum depression. Animal studies also indicate that low tissue or dietary n-3 polyunsaturated fatty acids can lead to neurobiological effects and behaviors associated with depression, whereas higher tissue levels or intake have the opposite effect. With the aim of determining the neurobiological effects of decreased brain dha content and its interactions with reproductive status, the effects of a 20-25% decrease in brain dha content, similar to that reported in depressed humans, induced by diet in adult virgin and reproducing female rats were examined. This treatment produced a number of neurobiological findings similar to those observed in depressed humans. Notably, in both virgin females and parous dams examined at the time of weaning, decreased brain dha resulted in reduced hippocampal brain-derived neurotrophic factor gene expression and increased relative corticosterone response to an intense stressor. Virgin females with decreased brain dha also exhibited decreased cortical serotonin content and turnover; whereas in parous dams, decreased brain dha resulted in

increased corticosterone response to an intense stressor and increased density of d_2 receptors in the nucleus accumbens. The latency to immobility in the forced swim test was also decreased in parous dams with decreased dha compared to parous dams with normal dha. These findings demonstrate an interaction between brain dha content and reproductive status in female rats, support a contributory role for reduced brain dha in the multifactorial pathogenesis of non-puerperal and postpartum depression, and suggest opportunities for clinical research and interventions. *Supported by NIH MH071599*.

Omega-3 deficiency impacts dopamine related functions. B. Moghaddam, S. Lotfi, S.R. Sesack, C. Flores, University of Pittsburgh; McGill University. Identifying mechanisms by which environmental factors affect the onset and course of psychiatric disorders is critical for their prevention and treatment. Nutritional factors, in particular dietary deficiency of omega-3 polyunsaturated fatty acids (n-3 PUFAs), have been implicated in the onset of schizophrenia and mood disorders in young individuals who are at high risk to develop these conditions. Animal models of this dietary deficiency in adolescents and adults are critical for understanding how n-3 PUFA deficiency influences overall behavioral health and symptoms of these illnesses. We recently developed such a model involving consecutive generations of n-3 PUFA deficiency based on the assumption that dietary trends toward decreased consumption of these fatty acids began four-five decades ago when the parents of current adolescents were born (Biological Psychiatry, 2014). In addition to behavioral disruptions that were augmented in the second generation (G2) of n-3 PUFA deficient adolescent animals, we observed changes in the expression of dopamine-related proteins that were different in adolescents as compared to adults. To expand on these findings, we have focused on assessing DCC and TH expression, as well as dopamine cell number and structural characteristics in these diet groups. DCC is a receptor for the axonal guidance cue netrin-1, and is involved critically in the adolescent developmental organization of dopamine connectivity. Previous work shows that changes in DCC expression lead to altered DA connectivity and function in a manner that is dependent on age and region. We find that DCC expression in G2 n-3 PUFA deficient adolescents is lower in the nucleus accumbens (NAc) and higher in the dorsal striatum (DS) compared to adequately fed counterparts. In G2 adult animals with n-3 PUFA deficiency, DCC expression in NAc and DS also is affected, but in an opposite direction from what is seen in adolescents: DCC expression is higher in NAc but lower in DS, as compared to adequately fed animals. Neuroanatomical analyses to determine potential alterations in dopamine cell number, somal size and ultrastructural features are ongoing.

Sphingolipids: from depression and anxiety to alcoholism Christian P. Müller[1], Thomas Stöckl[1], Eva Sprenger[1], Jens Tiesel[1], Sabine Huber[1], Davide Amato[1], Erich Gulbins[2], Martin Reichel[1], Johannes Kornhuber[1]. [1]Friedrich-Alexander-University of Erlangen-Nuremberg, Germany; [2]University of Duisburg-Essen, Germany. Alcohol addiction is a very common psychiatric disorder with severe health consequences for the individual and for society. A common aetiology is the depression/anxiety-induced alcohol addiction. Stress, or a particular susceptibility lead to a primary depression and anxiety. In an attempt to reduce this aversive state, controlled alcohol consumption can develop into alcohol addiction. The acid sphingomyelinase (ASM)-ceramide pathway has been shown to control the balance between neurogenesis and apoptosis in the brain. ASM hydrolyses the lipids sphingomyelin to ceramide and represents a major regulator of the sphingolipid metabolism. Genetically induced overexpression of ASM (tgASM) results in a depressive/anxious phenotype in mice. Here an overview is presented on how this pathway may facilitate the establishment of alcohol consumption and alcohol's reinforcing effects. We used tgASM and heterozygous ASM knock out (hetKO ASM) mice and tested alcohol preference and escalation of consumption after repeated withdrawals. Subsequently, we measured alcohol's acute locomotor effects, conditioned place preference (CPP), sensitization, and conditioned hyperlocomotion. We found a significantly enhanced alcohol preference in tgASM mice, which is persistent over time for 16 vol.% alcohol solution. After repeated withdrawals, tgASM mice showed massively enhanced alcohol consumption compared to baseline and wild type. HetKO ASM mice in turn showed a reduced alcohol preference at medium alcohol concentrations and attenuated consumption after repeated withdrawals. This was in line with a significantly reduced alcohol-induced CPP and locomotor sensitization in hetKO ASM mice. These findings suggest the ASM-ceramide pathway as a potential mediator of depression-

induced alcohol preference, and possibly, addiction. Acknowledgement: This work was supported by the Interdisciplinary Center for Clinical Research Erlangen, Project E13.

The modulatory impact of endocannabinoid signaling on adolescent drug abuse. Miriam Schneider**.** RG Developmental Neuropsychopharmacology, Central Institute of Mental Health, Mannheim, Heidelberg University, Germany**.** Puberty is a highly susceptible developmental period during which the organisation and the neuronal maturation of the brain, which began during perinatal development, are completed. During puberty an individual changes from a biologically non-reproductive, infertile juvenile into an adult who can reproduce. This stage is one of the major changes in biology and these maturational events and processes of reorganisation are needed for the occurrence of adult behavioral performance but also render the organism vulnerable to all sorts of disturbances. It is exactly during this developmental period that many neuropsychiatric disorders such as schizophrenia, mood and eating disorders, as well as drug abuse have their onset. Teenagers typically tend to seek out new stimuli during puberty, engange in risky behavior and show an increase in consummatory behavior for appetitive rewards and drugs of abuse. Therefore, puberty has been shown to represent a susceptible period for experimental drug use and it is known that the initation of substance abuse (e.g. alcohol abuse) during this developmental period is strongly associated with a higher risk for the development of addictive behaviors in later life. Along with the dopaminergic and the endogenous opioid system, the endocannabinoid system has emerged recently as a key neurochemical mediator of reward processes. It is well known that cannabinoids can induce euphoric and rewarding effects in humans and animals and growing evidence indicates that the endocannabinoid system modulates various aspects of drug and non-drug reward. Results from our animal studies indicate an important role for the developing endocannabinoid system during puberty in the modulation of reward sensitivity and the vulnerability towards drug abuse in teenagers.

6:00-8:00 Poster Session 1

1. **Age and gender relate to performance on a lexical decision task and change in negative affect in a population of daily smokers with elevated depressive symptoms.** Alexandra N. Houston-Ludlam, B.S.1, Avery D. Mitchell, B.S.1, Catalina Kopetz, Ph.D.2, Reinout W.H.J. Weirs, Ph.D.3, & Laura MacPherson, Ph.D.1. 1 University of Maryland, College Park. 2 Wayne State University. 3 University of Amsterdam. Lexical Decision Task (LDT) performance is often assessed in college-age samples with minimal observed error. Recent research in clinical, substance-using populations (Weirs *et al.*, 2011), and in the current sample of smokers with elevated depressive symptoms, has found error rates in excess of 30% for up to 15% of the sample. This erroneous data is discarded in reaction time analyses, but factors related to this error observed in substance using populations have yet to be identified. The goal of the present research was to identify demographic differences task performance within this sample. The sample included 67 adult daily smokers (42.0% female, 65.7% African-American, age M(SD)=45.6(13.7), baseline cigarettes/day M(SD)=12.8(6.2)) with elevated depressive symptoms (BDI-II ≥10) enrolled in a smoking cessation study. Participants completed at least three of four training sessions, which consisted of a negative mood induction (International Affective Picture Series; IAPS), retraining session using an Approach-Avoidance Task (AAT; Weirs *et al.*, 2011), and completion of a LDT in which participants were instructed to decide whether a phrase represented an "activity" or "not an activity," while in a state of negative affect. Positive and negative affect was measured pre- and post-IAPS presentation. Data were analyzed using partial correlations for the final training session of the study to account for familiarity with the study procedure. Age was inversely related to error in identifying smoking cues "activities" in the LDT after co-varying for cigarette consumption (r=.48, p<0.0001). Females showed greater change in negative affect induction following the IAPS when co-varying for initial negative affect (r=.36, p<0.004). High rates of error were due to incorrectly identifying smoking-related phrases as "not an activity." The differential response to the negative mood induction (IAPS) between men and women suggest that women are completing the training and task in a different mood state than men, which should be considered when evaluating the impact of the intervention. The current study aimed to increase cognitive activation of rewarding, non-smoking behavior, a hypothesized mechanism for change in smoking behavior, through an approach bias modification procedure (AAT). The expected outcome of this activation was increased RT to smoking cues and decreased RT to rewarding, non-smoking activity. Results suggest a

difference in how younger participants conceptualize smoking phrase cues. Thus, this intervention may benefit from explicit conceptualization of smoking and non-smoking behaviors in younger participants. Support: NIDA R01DA018730-05-F6; PIs MacPherson & Kopetz.

2. **Creatine transporter knockout mice show increased anxiety, increased depressive-like behaviors, and reductions in sociability.** Amanda N. Kokenge and Matthew R. Skelton. Division of Neurology, Cincinnati Children's Research Foundation; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45229**.** Creatine deficiency syndromes are a family of disorders characterized by intellectual disability, aphasia, and epilepsy. The most common cause of Cr deficiency is Creatine Transporter Deficiency (CTD) which is the second leading cause of X-linked intellectual disability (XLID). We have developed a high-fidelity model for CTD, the creatine transporter (CrT) knockout ($CrT^{-/y}$) mouse. While the primary goal of the work to date has focused on the cognitive deficits, it is important to evaluate affective behaviors in these animals. Cr has been implicated in depressive-like behaviors in the mouse and rat; therefore, we set out to determine if $CrT^{-/y}$ mice showed changes in anxiety and depressive-like behaviors. $CrT^{-/y}$ mice appeared to be more anxious than $CrT^{+/y}$ mice, spending less time in the open arms and committing fewer head dips in the elevated zero maze compared to $CrT^{+/y}$ mice. When tested in the tail-suspension test, $CrT^{-/y}$ mice had a decreased latency to immobility compared with $CrT^{+/y}$ mice, suggesting moderate depression-like behavior. Finally, sociability was reduced in the $CrT^{-/y}$ mice with $CrT^{-/y}$ mice spending less time with the novel stranger compared with $CrT^{+/y}$. These results suggest that Cr plays an important role in affective behaviors. Further, these results suggest that patients with Cr deficiencies need to be monitored for changes in these behaviors during treatment.

3. **Exercise tolerance as a predictor of recovery from concussion in adolescent athletes.** Andrea Hinds[1], John Leddy[1], John Baker[1], Barry Willer[1]. [1]University at Buffalo. Recovery from concussive injury is highly variable. There is of great interest from parents, educators, coaches, and trainers to successfully determine the risk of delayed recovery in student athletes on a case-by-case basis, but current standards for diagnosis and treatment of concussion make such predictions unreliable. We sought to determine whether a test of exercise tolerance during the acute phase after concussion would help to better predict recovery at 2-3 weeks post-injury. 50 adolescents (mean age 15.4, range 14-19 years) with recent concussion (mean 4.3 days since injury) were randomly assigned to either receive an evaluation of response to exercise (graduated stress test) or no intervention. Participants completed computerized cognitive testing and a symptom checklist, and reported symptoms daily for 14 days post evaluation. Heart rate (HR) and perceived exertion (RPE) at symptom exacerbation threshold during exercise determined exercise tolerance. All participants had an exercise stress test on follow up 2 weeks later. Logistic regression analysis determined which variables predicted recovery, defined as being asymptomatic, exercise tolerant (successfully exercising to exhaustion without symptom exacerbation), and positive evaluation by blinded physician assessment. After 2 weeks, only 6 of 25 participants randomized to the initial stress test and 5 of 25 participants that had not received this evaluation were still symptomatic. There was no significant difference in the daily symptom reports between the two groups. Gender, age, number of prior concussions, symptom severity, and scores on cognitive tests did not predict which athletes would be recovered at two weeks. In contrast, HR at threshold for exercise tolerance (measured in participants assigned an exercise stress test while acute) was the only variable that predicted recovery at 2 weeks ($R^2 = 0.493$; p=.000). Early systematic evaluation of exercise tolerance in adolescents after concussion, therefore, was essential in order to make this prediction. Exercise tolerance can safely be assessed early after concussion to establish short-term accurate prognosis for recovery. We gratefully acknowledge the support of The Robert Rich Family Foundation, The Buffalo Sabres Foundation, the Program for Understanding Childhood Concussion and Stroke, and The Ralph C. Wilson Foundation.

4. **Skipping breakfast disturbs early stages of cognitive processing. An ERP study.** González-Garrido Andrés Antonio[1,2], Brofman Epelbaum Jacobo José[1], Gómez-Velázquez Fabiola Rebeca[1],

Balart Sánchez Sebastián Agustín[1]. 1. Neuroscience Institute. University of Guadalajara, Mexico**.** 2. O.P.D. Hospital Civil de Guadalajara. It is generally accepted that skipping breakfast generates an adverse effect on cognitive processing. However, the benefits or disadvantages of short term fasting over the neural basis underlying cognition are far from be elucidated. The present study aimed to evaluate this issue by comparing the behavioral results and event-related brain potentials (ERP) during the performance of three working memory tasks (N-Back) in healthy subjects on both normal and mild-hypoglycemic conditions. Methods: Twenty young right-handed, healthy, university students (10 males and 10 females) participated in the experiment. In two morning sessions, all the participants performed 3 N-Back tasks in normal condition (previous breakfast) or mild hypoglycemia (twelve hours fasting) with simultaneous EEG recording. The blood concentration of glucose was measured immediately before the beginning of each experimental session. Results: Behavioral performances showed significantly fewer correct responses during hypoglycemia, mainly affecting the task in which working memory load was higher. The reaction times prolonged when task difficulty increased, regardless the blood level of glucose. The analysis of the ERP showed that mild hypoglycemia induced a significant decrement in the voltage magnitude of the N200 component, while the amplitude of P200 significantly increased. Conclusions: Behavioral and electrophysiological results suggest that the mild hypoglycemia due to skipping breakfast disturbs earlier steps in cognitive processing, particularly those involving attention allocation and typical shape information and this effect increases with task difficulty. In brief, the present study provides direct neurophysiological evidence about the negative impact of skipping breakfast on daily cognitive processing in healthy young people.

5. **Social defeat during adolescence escalates adult cocaine self-administration: Role of adolescent social experience and adaptive coping behaviors.** Andrew R. Burke and Klaus A. Miczek. Department of Psychology, Tufts University, Medford, MA, USA. Adverse experiences during adolescence increase the initiation of illicit drug use and the development of addiction. A history of brief intermittent confrontations with a highly aggressive conspecific (i.e. social defeat) promotes greater voluntary self-administration of cocaine in adult rodents, but has not been investigated after social defeat during adolescence. Social housing conditions during adult social defeat alleviate some negative behavioral and physiological outcomes, but the impact on drug self administration is unknown. Thus, we manipulated social experience (housing conditions) and stress history during adolescence and measured cocaine taking in adulthood. Adult residents are less aggressive toward adolescent rodents and the role of housing conditions on adolescent social defeat behaviors have not been studied. We also investigated the effect of age and housing on resident and intruder behavior during the first and last episode of defeat. Rats were housed in pairs (PH) or singly (SH) on postnatal day (P) 21 and then exposed to social defeat or control treatment from P35-44. We assessed novelty- and cocaine-stimulated locomotion in early adulthood (P57-61). Next, rats were fitted with intravenous catheters and acquired cocaine self-administration. This was followed by assessment of cocaine self-administration according to a fixed and progressive ratio schedule of reinforcement and then during a 24-hour continuous access binge. Residents were less aggressive toward PH adolescent intruders compared to PH adults. Furthermore, PH adults displayed defensive and supine postures when attacked, whereas PH adolescents froze. Adolescent PH rats adapted their behavior from the first to last defeat by increasing freezing behavior, while SH rats decreased freezing. A greater percentage of SH rats and PH defeated rats acquired cocaine self-administration compared to PH controls. Defeated PH rats consumed more cocaine during progressive ratio schedules and during the binge compared to both PH controls and SH defeated rats. Greater attack-induced freezing after repeated defeats predicted escalated cocaine self-administration in adulthood. Thus, social defeat in adolescence, while different than during adulthood, still increased cocaine taking in PH, but not SH rats. Coping with attacks adaptively over repeated confrontations characterized adolescent PH rats and predicted adult cocaine taking. Support: NIH R01DA031734 (KAM), NIH F32DA032226 (ARB)

6. **An evaluation of peripheral insulin disruption on behavior, phosphorylated tau levels, and microglia activity.** Andrew S. Murtishaw1, Chelcie F. Heaney1, Monica M. Bolton1, Krystal Courtney D. Belmonte1, Michael M. Langhardt1, Jefferson W. Kinney1. 1University of Nevada, Las Vegas. Diabetes Mellitus (DM) has been identified as a major risk factor for developing Alzheimer's disease

(AD) and vascular dementia (VaD). While DM is a complex metabolic disorder with many associated symptoms and complications, disrupted insulin signaling has been implicated as the aspect most likely making DM a risk factor for dementia-related diseases. Much research has been conducted using streptozotocin (STZ), a compound that targets and destroys insulin producing pancreatic β-cells, to better understand DM. Additionally, the administration of STZ has been used to model sporadic Alzheimer's disease due to its ability to alter behavior and hyperphosphorylated tau in the brain. Much of the DM research utilizing STZ relies on the administration of very high single dose or repeated daily doses of a slightly lower dose, both of which are often associated with an increased mortality rate and renders sick animals not optimal for behavioral testing — particularly sensitive learning and memory tasks. The purpose of this experiment was two fold. First, we set out to create an optimal dose schedule to be administered over the course of several weeks that would lead to a viable and sustainable diabetic state, including the elevation of blood glucose levels, alterations in learning tasks, and dementia-related protein changes, while eliminating the increased mortality rate and maintain physically healthy rodents. Second, microglia activity is not well-documented following peripheral STZ administration; therefore we investigated the effect of peripheral STZ on microglia in several areas of the hippocampus, hypothalamus, and the cortex. We were able to create an optimized multiple low-dose STZ administration schedule, over the course of 15 days, that lead to significantly elevated blood-glucose levels and overall healthy animals following a battery of standardized behavioral tests. Starting the sixth week after the first STZ injection, animals were assessed for learning and memory in the open field and Novel object recognition tasks, following which brains were removed and prepared for either western blotting to investigate tau pathologies in the cortex and hippocampus or for immunohistochemistry to evaluate microglia activity in the cortex, hippocampus, and hypothalamus.

7. **Relaxin-3/RXFP3 networks in food intake and stress responses – neural mechanisms underlying behavioural effects.** Anna Blasiak1, Alan Kania1, Marian H. Lewandowski1, Andrew L. Gundlach2**.** 1Department of Neurophysiology and Chronobiology, Jagiellonian University, Krakow, Poland, 2The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Australia**.** An overabundance of stressors in everyday life and free access to highly-rewarding, high-caloric foods are considered significant causes of obesity in modern societies. Indeed, obesity is a leading preventable cause of death globally; so a better knowledge of neural mechanisms responsible for disturbances in energy homeostasis that lead to eating disorders is important. However, the identity of all the neurochemicals and neural substrates underlying stress and reward-related behaviours is not known and effective treatments of obesity are still required. Soon after its discovery, the first identified physiological effect of icv injections of the neuropeptide, relaxin-3, was an increase in food intake in satiated adult rats, with a similar potency to canonical orexinergic peptides such as NPY. Furthermore, relaxin-3-expressing neurons located in the nucleus incertus (NI) within the posterior ventromedial central grey, are responsive to a range of stressors, making the relaxin-3 system a good candidate for linking stress and stress-related feeding. However, the nature of interactions between NI/relaxin-3 neurons and other neural circuits controlling energy homeostasis and stress responses remain largely unknown. Among brain areas innervated by NI neurons, the hypothalamic paraventricular nucleus (PVN) was implicated in relaxin-3-mediated food intake; and the effects on feeding of acute and chronic intra-PVN administration of native relaxin-3 or potent relaxin-3 receptor (RXFP3) agonist peptides, is thought to be mediated by inhibition of hypothalamic oxytocin (OT) and vasopressin PVN neurons (Ganella DE et al., Behav Pharmacol 23 (2012) 516-25). Recent in vitro brain slice experiments demonstrate an potent inhibitory action of RXFP3 agonists (RXFP3-A2, 600 nM) on PVN neurons (42 of 67 neurons tested). Importantly, these effects are direct since they persist in the presence of TTX (1 µM) and glutamate and GABA receptor blockers (10 µM). Notably, several inhibited cells were identified as magnocellular oxytocin-positive neurons and RXFP3 agonist-induced inhibition of parvocellular neurons was also observed. Our data support the hypothesis that relaxin-3/RXFP3 signalling is associated with stress and feeding-related abnormalities, including obesity and binge eating and we are currently exploring further behavioural

effects of hypothalamic RXFP3 activation under different dietary and stress conditions. Funding: National Science Centre Poland DEC-2012/05D/NZ4/02984 and Ministry of Science and Higher Education, Poland 0020/DIA/2014/43.

8. **Long-term exposure to high corticosterone levels enhances glutamatergic but does not alter GABAergic transmission in the rat motor cortex.** Anna Błasiak1, Joanna Kula1, Anna Czerw1, Grzegorz Tylko1, Grzegorz Hess1,2**.** 1 Institute of Zoology, Jagiellonian University, Gronostajowa 9, 30-387 Krakow, Poland**.** 2 Department of Physiology, Institute of Pharmacology, Polish Academy of Sciences, Smetna 12, 31-343 Krakow, Poland**.** Repeated stress experience and resulting exposure to high levels of corticosteroid hormones are a major risk factors in serious pathologies including depression, cognitive impairments and motor control dysfunctions. Animal models of repeated stress such as restraint stress, are sensitive to procedural differences between experiments and habituation of animals to the stress procedures. Recognized as non-adaptive, repeated stress procedure analogue that reliably evoke depression-like behavior in a dose-dependent manner, are repeated corticosterone administrations. We studied the effects of single and repeated injections of corticosterone on spontaneous excitatory and inhibitory postsynaptic currents (sEPSCs and sIPSCs) recorded from layer II/III pyramidal neurons in ex vivo slices of the rat frontal cortex, prepared 2 days after the last administration of the hormone, and on the protein density levels of selected subunits of AMPA, NMDA and GABAA receptors. Corticosterone administered repeatedly for 7 days induced an increase in the frequency but not the amplitude of sEPSCs, but single administration of corticosterone remained without effect. The frequency and amplitude of sIPSCs as well as the excitability of pyramidal cells remained unchanged after corticosterone administration. Treatment with corticosterone did not modify the density of dendritic spines on pyramidal neurons. Treatment with corticosterone influenced neither the protein density levels of GluA1, GluA2, GluN1, GluN2A and GluN2B subunits of ionotropic glutamate receptors nor that of α1, β2 and γ2 subunits of the GABAA receptor. Repeated corticosterone-induced increase in sEPSCs frequency faded out within 7 days. These data indicate that prolonged administration of exogenous corticosterone selectively and reversibly enhances glutamatergic, but not GABAergic transmission in the rat frontal cortex and suggest that corticosterone treatment results in an enhancement of spontaneous glutamate release from presynaptic terminals. Support: grant UMO-2012/07/B/NZ4/01669 financed by the Polish National Science Centre.

9. **Muscimol applied to the dorsolateral periaqueductal gray matter impairs the negative valence instruction from a stressful experience**. Antonio P Carobrez , Marcelo Giachero. Departamento de Farmacologia/CCB – Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil. Stress exposure induces long lasting neurobiological changes in selected brain areas, which could be associated with the emergence of negative emotional responses. A growing number of evidence has revealed that the interaction of a stressful experience and the retrieval of an established fear memory trace enhanced both fear expression and fear retention. Related to this, a negative emotional state elicited by the stimulation of the dorsolateral periaqueductal gray (dlPAG) prior to retrieval potentiates a fear memory trace previously acquired. Therefore, the question that arises is whether the PAG mediates the increased fear expression and fear retention after retrieval? Adult male Wistar rats were subjected to a contextual fear conditioning paradigm using a single footshock (weak training session). One day after training, rats were subjected to a stressful situation (restraint for 30 min.). Animals were re-exposed to the original context of conditioning (Test 1) for 3 minutes one day after the stress. There was an increase of freezing only in those animals re-exposed to the associated context, which persisted in the Test 2 performed 6 days after stress exposure. Muscimol intra-dlPAG previous to conditioning or restraint prevented such increase. Conversely, Muscimol intra-dlPAG infusion immediately after conditioning or restraint did not affect the resulting fear memory. In conclusion, the present results suggest that the dlPAG is a key neural site for negative valence instruction able to modulate the promoting influence of stress on fear memory. Moreover, the dlPAG emerges as a key site to respond to life threatening events and, at the same time, to influence the incoming instruction

for aversive coding experience, but not as a relevant structure for mnemonic stabilization. Financial Support: CAPES, CNPq, UFSC.

10. **Opioid modulation of responses to social rejection in humans.** Bershad, Anya K1,2 and de Wit, Harriet2**.** 1Interdisciplinary Scientist Training Program, University of Chicago, Chicago, IL USA; 2Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL USA**.** In addition to its classical role in mediating responses to pain, the opioid system is strongly implicated in the regulation of social behavior. It has been suggested that the brain networks mediating responses to social distress may have evolved from more primitive pain-processing circuitry, and neuroimaging evidence suggests that social rejection or “social pain” and physical pain activate similar neural networks. In young laboratory animals, low doses of opioid analgesic drugs reduce responses to isolation distress, and enhance responses to some types of social reward. However, it is not known how opioid analgesic drugs affect responses to social stimuli in humans. Here we examined the effects of buprenorphine, a μ-opioid partial agonist used to treat opioid dependence and pain, on responses to simulated social rejection in healthy young adults. We hypothesized that buprenorphine would reduce the subjective experience of social rejection, and that it would preferentially affect responses to social stimuli over other types of affective stimuli. Healthy adult volunteers (N = 36) attended two laboratory sessions during which they received either placebo or 0.2mg sublingual buprenorphine in randomized order, under double-blind conditions. Ninety minutes after drug administration, volunteers participated in a virtual ball-toss game in which they were first included and then excluded by the other players. They also completed a picture-viewing task, in which they rated standardized positive, negative, and neutral images with and without social content, and during which psychophysiological measures of emotional reactivity were obtained. Throughout the sessions, measures of subjective drug effect and mood, heart rate, and blood pressure were collected at regular intervals. Compared to placebo, buprenorphine significantly increased participants’ estimates of the number of times they received the ball during the ball-toss task, suggesting a decreased sensitivity to exclusion. The drug also significantly increased positive emotional responses to images with social content, without affecting ratings of nonsocial images. These results suggest that even at low doses, opioid analgesic drugs reduce perception of social exclusion, and preferentially influence responses to social affective stimuli. These findings provide further support for the role of the opioid system in mediating responses to social rejection. This research was supported by NIDA DA02812.

11. **Major impact of the first-line antiepileptic treatment choice on the second-line treatment efficacy in a mouse model of absence epilepsy.** Martin Benoît1,2, Kuchenbuch Mathieu3,4, Hadjadj Sarah3, Dieuset Gabriel1,2, Costet Nathalie1,2, Javaudin Loïc5, Wendling Fabrice1,2, Biraben Arnaud1,2,6. 1INSERM, U1099, 35000 Rennes, France, 2Université de Rennes 1, Laboratoire de Traitement du Signal et de l'Image (LTSI), 35000 Rennes, France, 3Département de Neurologie Pédiatrique, CHU Rennes - hôpital sud, 35203 Rennes, France, 4Département des Explorations Fonctionnelles Neurologiques, CHU de Rennes-Pontchaillou, 35000 Rennes, France, 5Unité de Pharmacologie, CHU de Rennes-Pontchaillou, 35000 Rennes, France, 6Département de Neurologie, CHU de Rennes-Pontchaillou, 35000 Rennes, France. Possible aggravation of epilepsy by antiepileptic drugs is an already known phenomenon. Overdoses and drug interactions are the two main reasons. However, seizures can also be worsened because of an inadequate treatment. This is often the case for children epilepsies such as childhood absence epilepsy. We addressed the problem of whether an inadequate first-line treatment could abolish the efficacy of a second-line treatment that would have been successful if applied as a first-line treatment. We used an inbred mouse model for absence epilepsy, BS/Orl, manifesting spontaneous and recurrent spike-wave discharges. Mice were submitted to an experimental protocol where they received two consecutive treatments. From the age of five weeks, mice were given valproate (VPA - reference), vigabatrin (VGB - known to aggravate the absence epilepsies) or ethosuximide (ESM - a specific for absence epilepsies) during 14 days. And then, they all received VPA during 42 days. A fourth group has received a saline solution (PHY) during the whole experiment. The 4 groups were assessed at 5

different times: before any treatment, after the first-line treatment and 3 times during the second-line treatment. After the first-line treatment, the 3 groups VPA, VGB and ESM were differing significantly as expected: compared to PHY, VGB was found to worse seizures whereas VPA and ESM were found to reduce seizures with a much greater effect for ESM. Interestingly, the application of the second treatment showed various effects. While the seizure level in the ESM group was much lower than in the VPA group after the fist-line treatment, this benefit has progressively disappeared with the introduction of the VPA. Finally, after 6 weeks of VPA treatments, both ESM-VPA and VPA-VPA were presenting the same seizure occurence rate. Conversely, while the VGB has aggravated the seizure level compared to the PHY group during the first-line treatment, the introduction of the VPA as the second treatment, has failed to reverse the tendency of an aggravation of the seizure level due to the initial application of the VGB. This study illustrates that an inadequate first-line treatment, more than worsening seizures, can have long-term adverse effects by reducing the efficacy of a posterior treatment.

12. **Conditioned object preference: a novel measure of drug-seeking in rodents.** Bruce C. Kennedy1, Maulika Kohli2, Jamie Maertens2, Paulina Marell3, Jonathan C. Gewirtz1,2. 1Graduate Program in Neuroscience, University of Minnesota. 2Department of Psychology, University of Minnesota. 3Department of Neurobiology, University of Pittsburgh. Conditioned place preference (CPP) is a commonly used task in rodents to measure the subjective rewarding qualities of experiences such as exposure to drugs of abuse. In this task, preference for an environment is acquired through associative learning following repeated pairings with a pleasurable experience. Studies in humans have demonstrated that similar to environments, reward-paired objects such as drug paraphernalia can elicit a conditioned response. However, the ability of objects to serve as conditioned stimuli has yet to be explored in rodents, despite the advantage of greater stimulus control when using this approach compared with CPP. We present here initial findings from a novel task, Conditioned Object Preference (COP) in which we measured the preference of adult male Sprague Dawley rats for objects paired with cocaine administration. We first measured investigation of test objects to establish baseline object preference which was followed by two to six days of conditioning, alternating daily between saline and cocaine treatment. During this phase, rats were injected with either saline or cocaine (20 mg/kg, intraperitoneal (ip)) and placed into the test chamber containing two copies of the same object for 30 minutes. Different objects were paired with cocaine vs. saline and several different object sets were used for conditioning. Following two, four, or six days of conditioning, rats received additional tests for object preference in a drug-free state in order to measure the acquisition of COP. We observed that rats investigated the cocaine-paired object significantly more than the saline-paired object after as few as two drug-object pairings, indicating acquisition of cocaine-paired object preference. This preference occurred regardless of which object was paired with cocaine, suggesting that COP can be acquired for many different types of objects. Following acquisition, extinction of COP was performed using daily tests for object preference in the absence of cocaine. During extinction, object preference returned to baseline levels but COP was reinstated with a priming dose of cocaine (10 mg/kg, ip). These findings demonstrate that similar to environments, objects can elicit conditioned approach behavior through associative learning. Furthermore, COP is amenable to the demonstration of the Pavlovian phenomena of extinction and drug-primed reinstatement. Considering the greater stimulus control afforded by objects, the COP task could be applied toward novel approaches to assessing drug-seeking behaviors in rodents.

13. **Adolescent antidepressant treatment induces an enduring anxiogenic behavioral phenotype in adulthood.** Bryan Cruz1, Kristi L. Shawhan1, Ricardo Rodriguez1, Norma N. Zamora1, Raisa Ahmed1, Mirella Hernandez1, Lisa Motley1, Sergio D. Iñiguez1**.** 1California State University of San Bernardino, Department of Psychology**.** Until recently, the existence of major depressive disorder (MDD) in children and adolescents was not well recognized. Now, epidemiological reports indicate that MDD is quite common in the young. Unfortunately, with the increasing number of children and adolescents being diagnosed with MDD, a disproportionate increase in fluoxetine (FLX) is being

prescribed to this population. Because treatment duration for MDD can last for years, it is surprising that not much is known about the long-term consequences of antidepressant treatment during critical developmental periods. To examine this at the preclinical level, we conducted a series of experiments where we exposed adolescent male c57BL/6 mice to FLX (20 mg/kg) for 15 consecutive days (postnatal days 35-49). We then assessed the ability of FLX to influence responses to anxiogenic stimuli when animals reached adulthood (postnatal day 70). Specifically, adult mice pretreated with FLX during adolescence were exposed to the anxiogenic environment of the elevated plus maze, open field test, and the novelty induced hypophagia paradigm. Our results show that FLX exposure during adolescence results in an increased sensitivity to anxiogenic-like behaviors in adulthood. Collectively, these data suggest that early-life FLX pretreatment induces a heightened sensitivity to anxiety-inducing situations later in life. Funding was supported by NIDA R24DA033877, CSU Program in Education and Research in Biotechnology, and Associated Students Inc. Grant from CSUSB.

14. **Reduced levels of Cacna1c modify mesolimbic dopamine system function.** Terrillion CEa,d, Dao, DTa, Cachope Rb, Lobo MKa,b,d, Puche, ACb,d, Cheer JFa,b,d, Gould TDa,b,c,d. aDepartment of Psychiatry, bDepartment of Anatomy and Neurobiology, cDepartment of Pharmacology, dProgram in Neuroscience, University of Maryland School of Medicine. CACNA1C codes for the L-type calcium channel Cav1.2, and has been associated with clinical diagnoses of bipolar disorder, schizophrenia, and depression. L-type calcium channels are associated with normal function of the mesolimbic dopamine (ML-DA) system, dysregulation of which is linked to these disorders. We hypothesized that reduced levels of Cav1.2 leads to decreased ML-DA system function, resulting in attenuation of a subset of DA mediated behaviors. Methods: Cacna1c heterozygous (HET), wild-type (WT), and Cre-dependent conditional Cacna1c knock-out mice were tested in several behaviors following stimulant challenge, including acute locomotor response, sensitization, conditioned place preference (CPP), and stereotypic behavior. Using fast-scan cyclic voltammetry (FSCV), DA release and reuptake in the NAc of HET and WT mice was measured following stimulation of the ventral tegmental area (VTA). Recordings were taken following saline and GBR12909 administration. Western blot was used to determine levels of dopamine transporter (DAT) and other proteins. Results: Compared to WT littermates HET mice manifested significantly reduced hyperlocomotion following acute administration of stimulants specific to DAT (amphetamine, cocaine, and GBR12909) but not to glutamate (MK-801), as well as attenuation of sensitization to GBR12909. Knock-down of Cav1.2 in the VTA or NAc revealed that sensitization was blocked only in mice with reduced levels of Cav1.2 in the VTA. There was no effect of reduced Cacna1c levels on stereotypic behavior or CPP. FSCV revealed that HET mice had significantly more rapid DA reuptake after GBR12909 administration compared to WT mice. There was no effect of genotype on DAT protein levels. Conclusions: Cacna1c haploinsufficiency was associated with attenuation of selective DA dependent behaviors, and Cav1.2 in the VTA was found to mediate sensitization. FSCV revealed that Cav1.2 has a role in presynaptic ML-DA system function, including a possible role in regulating DAT activity. However, this is not due to total levels of DAT protein, suggesting that DAT activity is regulated through an alternative mechanism.

15. **Genetic difference in serial reversal learning in mice.** C.J. Heyser. Department of Neuroscience, University of California, San Diego, La Jolla, CA 92093. The behavioral differences described among genetically distinct strains of mice can be highly influenced, even dependent, on the methodology employed. Here we report the results of a series of experiments using two commonly used procedures: discriminated avoidance learning and discriminated operant learning. Avoidance learning was examined using a discriminated Y-maze task. This task measures the ability of the animal to discriminate between right and left and to initiate a response in order to avoid a negative outcome (footshock). A similar discrimination was examined in the operant task, where mice were trained to respond to either the left or right nosepoke in order to receive an appetitive outcome (20 mg food pellets). In addition, serial reversals were conducted in each of these procedures using either a history-based procedure (each reversal was conducted after a set number of trials) or on a criterion-

based procedure (each reversal was conducted only after the mouse had reached a specified performance criterion). Adult male Balb/cByJ, C57BL/6J, DBA/2J and C57BL/6xSJL F1 hybrid mice were used in these experiments. The results of the avoidance task showed that all mice acquired the initial task equivalently, whereas strain differences were observed during the serial reversals. C57xSJL mice showed significant positive transfer across reversals (i.e., acquisition occurred more quickly with each reversal) using a history-based procedure. This type of "savings" was observed in the Balb/cByJ mice, but to a lesser degree. DBA mice did not show any transfer effects, but rather displayed a similar pattern of acquisition across each reversal. In contrast, using a criterion-based reversal procedure, DBA mice exhibited significant savings during reversal learning, with all strains showing comparable performance across reversals. Similar results were obtained for operant conditioning, with parameter-dependent differences among the strains being observed during the serial reversal phase. Taken together with previous data from our lab, strain differences in learning are reliability observed. However, it is important to note that the differences in performance can (in some cases) be effectively eliminated by altering the training parameters of the task. Therefore, it is critical to continue to characterize basic behavioral profiles across a wide variety of tasks in genetically distinct populations of mice.

16. **Influence of adversity on maternal behavior of mothers that consumed alcohol during pregnancy: Short- and long-term effects on offspring.** Charlis Raineki; Parker J. Holman; Samantha Baglot; Dylan C. M. Yeates, Vivian Y. Y. Lan; Wayne Yu; Joanne Weinberg. Department of Cellular and Physiological Sciences, University of British Columbia, Canada. Alcohol consumption during gestation can alter the developmental trajectory of the fetus, leading to enduring emotional, physiological, cognitive, and neurobehavioral deficits. Moreover, the quality of the postnatal environment also plays a role on the development of the offspring. Indeed, early-life adversity can increase vulnerability to later mental and physical problems. Despite remarkable progress characterizing effects of prenatal alcohol exposure (PAE), relatively few studies have investigated how postnatal environmental adversity may alter maternal behavior, which, in turn, could contribute to the pervasive, long-lasting effects of PAE. Here, we combine two rodent models to examine the unique and/or interactive effects of PAE and early-life adversity on maternal behavior and offspring emotionality. Pregnant rats were assigned to either PAE – liquid ethanol diet ad libitum; Pair-fed (PF) – liquid control diet yoked to PAE consumption; or Control – pelleted control diet ad libitum. To model early-life adversity, half of these mothers were exposed to a limited bedding environment from postnatal day (P) 8-12, during which we recorded maternal behavior and pup vocalizations. Male and female offspring were tested in tasks assessing anxiety- (open field [OF] and elevated plus maze [EPM]) and depressive-like (forced swim test - FST) at P30 or P45. Insufficient bedding induced abusive-like maternal behavior across all groups. However, PAE pups vocalized less in response to early-life adversity. Our preliminary analyses of the OF indicate that PAE increased anxiety-like behaviors in females and early-life adversity increased anxiety-like behaviors in control females. Similar to the OF, we observed differential effects of PAE and early-life adversity in the EPM, and FST. Our results indicate that despite similar abuse-like maternal behaviors across prenatal groups, PAE pups vocalize less in response to early-life adversity. Moreover, results from later-life emotional behaviors demonstrate, unique and interactive effects of PAE and early-life adversity. Supported by NIH/NIAAA grants R37AA007789 and R01AA022460, and NeuroDevNet to JW, and Canadian Foundation on Fetal Alcohol Research (CFFAR) grant to CR and JW.

17. **Intermittent access to palatable foods: a comparison of sugar, fat and sweet-fat food consumption in adolescent male and female rats.** Christine M. Tenk1,2, Tina Felfeli2,3, Allison S. Adrian1. 1Department of Psychology, Brescia University College. 2Department of Psychology, Western University. 3Schulich School of Medicine and Dentistry, Department of Physiology and Pharmacology, Western University. London, ON, Canada. Binge eating is defined as larger or more rapid consumption of food than is typical under similar circumstances. Binging behaviour has been linked with obesity and its presence in several eating disorders makes it the most common eating

disturbance. In humans, most binge eating involves consumption of highly palatable foods that are rich in sugar, fat or both. In animal models, intermittent access to these same palatable foods has been used to effectively elicit binging behavior though some data suggest different responses to foods high in sugar compared to those high in fat. The aim of the current study was to compare the development of binging behavior in response to a variety of palatable foods in non-food deprived adolescent rats and to probe for associated sex differences. Adolescent female and male Long-Evans rats were given two-hour access to one of four foods (sugar, fat, sweet-fat, or standard lab chow) three times per week. Consumption of intermittently available food, as well as freely available lab chow was examined for five weeks. Results of this study highlighted the unique characteristics of binging behaviour induced by a sweet-fat food when compared to sugar and fat alone. That is, only animals consuming sweet-fat showed significant increases in consumption during the first week of access. Additionally, the sweet-fat group consumed significantly more during intermittent access than all other groups, and showed a greater decrease in chow consumption outside of intermittent access. Taken together, these results support the idea that binging behaviour toward sweet-fat foods is distinct perhaps as result of the macronutrient combination, texture or effect on brain reward pathways. Sex dimorphisms in binge eating behaviour were also observed in the current study with females demonstrating greater susceptibility to palatable food consumption and less of a decrease in chow consumption. These data will be critical for future investigations examining the underlying neural circuitry of binge eating, and the ultimate understanding and treatment of this disordered eating pattern in humans.

18. **Increased basal and stress-induced cortisol levels are associated with accelerated cellular aging in middle-aged women.** Barha, CK1; Salvante KG1,2; Hanna CW3,4; Wilson SL3,4; Robinson WP3,4; Nepomnaschy PA1,2. 1Faculty of Health Sciences and 2Human Evolutionary Studies Program, Simon Fraser University, Burnaby, BC Canada; 3Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada; 4Child and Family Research Institute, Vancouver, BC, Canada. Chronic stress has been proposed as one of the key modulators of the pace of aging. At the cellular level, stress may accelerate the manifestation of age-associated pathologies by increasing the pace at which telomeres shorten. Previous work has shown that exposure to psychological stress is related to shorter telomeres. A very limited number of studies have investigated whether telomere length of peripheral blood mononuclear cells are associated with psychological stress-induced cortisol levels and baseline cortisol levels, but no studies have looked at the relationship between overall basal activity of the hypothalamic-pituitary-adrenal (HPA) axis and change in telomere length over a long period of time. The present study extends this limited literature by examining how basal HPA axis activity, evaluated in first morning urinary specimens collected over a 6-week period, and HPA axis reactivity, evaluated as salivary cortisol response to a physical stressor, are associated with cellular aging in a cohort of middle-aged women. Specifically, current length of telomeres in epithelial cells as well as the rate of change in telomere length over a 13-year period were measured. Elevated basal first morning urinary cortisol and stress-induced salivary cortisol were associated with shorter current telomere length and greater shortening of telomeres over time in women. These findings provide further evidence of the importance of basal HPA axis activity and HPA axis reactivity as modulators of cellular aging. This work was supported by an operating grant and a post-doctoral fellowship from the Canadian Institutes of Health Research to PAN and CKB, respectively.

19. **Neuropathological Changes in Concussion.** Ciro Visone, Alliant International University**.** Research has shown concussions to trigger a series of neuropathological changes in the brain responsible for cognitive dysfunction. After impact, the brain undergoes an intense shift in metabolism known as a neurometabolic cascade responsible for initial symptoms (Giza & Hovda, 2001; Giza & Hovda, 2014). The brain enters a period of hyperglycolysis requiring an increase in energy to restore ionic imbalance (Yoshino et al., 1991; Marshall, 2012). Concussive injury distorts this supply and demand process of ATP causing difficulties in regulating ionic exchange. This releases glutamate-triggering N-

methyl-D-aspartate (NMDA) and Gamma-Aminobutyric acid (GABA), eliciting the accumulation of K+ ions outside of the cells while excessive Ca2+ enters the cell (Giza & Hovda, 2014). The disruption of K+ and Ca2+ impairs mitochondrial function. In the most severe cases the buildup of Ca2+ causes axonal tearing (DAI) and may alter neuroplasticity in hippoccampal cells (Santa Maria, & Hovda, 2006; Bashir et al., 2012). Psychological implications include difficulty with learning ability and memory, which may affect academic and intellectual functioning. A period of decreased cerebral blood flow and diminished need for energy conversion results in hypoglycolysis (Giza & Hovda, 2014).This produces cognitive, physical, and emotional symptoms including language and communication deficits (Hart et al., 2013). Moreover, in its attempt to salvage damaged brain tissue, inflammation-triggering cytokines have been identified at the site of the injury (Szmydynger-Chodobska et al., 2012). This has been linked to chronic cognitive problems and neurodegenerative brain disease because of their role in neuronal death. Furthermore, consequences do not always reflect cumulative injuries. Studies show alterations after a single episode (Zhou et al., 2013). Evidence reflects white mater atrophy 1 year post injury in the cingulated gyrus and precuneas marked by difficulties with attention and concentration, memory and mood regulation (Zhou et. al, 2013). By understanding the neurobiological changes in concussive injury, professionals can efficiently treat patients cognitively and physically. Rehabilitation can be specifically tailored. Most importantly are the implications for future brain disease. As the different neurosciences advance, a holistic approach can be taken at not only treatment, but the prevention of neurodegeneration.

20. **Relaxin-3/RXFP3 signalling promotes motivational drive and stress resilience in mice.** Craig M Smith1,2,4, Ihaia T Hosken1,4, Andrew W Walker1,2,4, Berenice E Chua1, Cary Zhang1,4, Derek A Denton3, Michael J McKinley3, Andrew J Lawrence2,4, Elena Timofeeva6, Andrew L Gundlach1,2,4,5**.** 1Neuropeptides, 2Behavioural Neuroscience and 3Neurophysiology Divisions, The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia, 4Florey Department of Neuroscience and Mental Health and 5Department of Anatomy and Neuroscience, The University of Melbourne, Melbourne, Australia, 6Department of Psychiatry and Neuroscience, Laval University, Quebec, Canada**.** The neuropeptide relaxin-3 is expressed by broadly projecting neurons within the pontine nucleus incertus, and signals through its widely expressed G-protein coupled receptor, RXFP3. Anatomical and functional evidence indicates that relaxin-3/RXFP3 signalling can modulate a range of limbic, septohippocampal, and hypothalamic circuits to influence motivation, stress responses, and other modalities related to behavioural arousal. Our studies have used transgenic and wild-type (WT) mice, in combination with newly developed pharmacological and viral tools, to further investigate the role of relaxin-3/RXFP3 signalling in behavioural control. Firstly, motivational drive was assessed. Central injections of RXFP3 antagonist reduced motivated food seeking ($p<0.05$) and consumption ($p<0.001$) in WT mice, while in salt (sodium) depleted WT mice, RXFP3 antagonist treatment reduced the motivation to consume a 0.3 M NaCl solution ($P<0.001$) – an effect also observed in sheep ($P<0.001$). Furthermore, relaxin-3 and RXFP3 knockout (KO) mice displayed reduced motivation to run on voluntary home-cage running wheels ($p<0.001$), and to press a lever to obtain sucrose reward in an operant chamber ($p<0.05$). Secondly, stress resilience was assessed, revealing that relaxin-3 and RXFP3 KO mice were hypersensitive to stress-induced insomnia ($p<0.001$) and stress-induced changes in alcohol consumption ($p<0.05$), respectively. Furthermore, central infusion of an RXFP3 agonist reduced elevated levels of anxiety-like behaviour induced in WT mice by the benzodiazepine receptor inverse agonist, FG-7142. To better determine the potential mechanisms which underlie these actions, the neurochemical phenotype of RXFP3 neurons was assessed using mice which express yellow fluorescent protein within RXFP3-positive neurons (RXFP3-eYFP). These studies have revealed some important insights. For example, relaxin-3/RXFP3 signalling may influence hippocampal activity via modulation of calretinin positive neurons within the hilar region of the ventral dentate gyrus. Taken together, these studies provide further evidence that relaxin-3/RXFP3 signalling influences key neuronal circuits to promote motivational drive and stress resilience. As these modalities are often disrupted in affective disorders such as depression, these studies highlight the potential of relaxin-3/RXFP3 systems as a therapeutic target.

21. **The evolution of brain structure in dragon lizards.** Daniel Hoops1, Jeremy F. P. Ullmann2, Andrew L. Janke2, Marta Vidal-Garcia1, Timothy Stait-Gardner3, Yanurita Dwihapsari3, William S. Price3, Martin J. Whiting4 & J. Scott Keogh1.1 Evolution, Ecology and Genetics; Research School of Biology; The Australian National University; Acton, ACT, 2601; Australia. 2 Center for Advanced Imaging; The University of Queensland; Brisbane, QLD, 4072; Australia. 3 Nanoscale Organization and Dynamics Group; School of Science and Health; University of Western Sydney; Penrith, NSW, 2751; Australia. 4 Department of Biological Sciences; Discipline of Brain, Behavior and Evolution; Macquarie University; Sydney, NSW, 2109; Australia. Many phenotypic traits such as behaviour, body shape, and colour are shaped by a combination of both natural and sexual selection. However, the two evolutionary processes often act in opposition. Natural selection usually acts to improve fitness by increasing survival. In contrast, sexual selection acts to improve fitness by increasing the likelihood of successful mating. This often results in characters, such as conspicuous ornaments and breeding colours, that seem to reduce survival. The interaction between these two modes of selection has been well studied for many traits, but the relative effects of natural and sexual selection on brain evolution is still relatively unknown. How does each type of selection influence brain structure? And how do the relative roles of natural and sexual selection compare to those on other traits closely associated with fitness such as colouration, body size, and key life history traits? To test the interaction between natural and sexual selection, we used high-resolution magnetic resonance imaging combined with traditional histology to document brain structure in 14 lizard species belonging to the Australian genus Ctenophorus (known as dragons). These species exist in discrete ecological types or “ecotypes”, which are behaviourally distinct, and vary in the strength of sexual selection they experience, which also influences their behaviour. At the level of major brain regions we found only evidence of natural selection acting on brain structure. However, when examining specific brain nuclei that are directly involved with reproductive behaviours we also found evidence that sexual selection has shaped the structure of the brain. We show that both natural and sexual selection have affected the evolution of brain structure.

22. **Unilateral Implantation Of Dopamine In The Caudate Nucleus Attenuates Motor Abnormalities In The Model Hemiparkinsonism In The Rat.** Vázquez Matías Daniel Aarón1, Valverde Aguilar María Guadalupe3, Mayen Díaz Rodrigo1, Sánchez Cervantes Ivonne Grisel2, López Martínez Irma2 , Colín Barenque Laura2, Velázquez Paniagua Mireya1, and Vergara Aragón Patricia1. 1.Physiology and 2.Cell and Tissue Biology Department, Faculty of Medicine. Universidad Nacional Autónoma de México. 3 Legaria Unit CICATA, Instituto Politécnico Nacional. Background: Parkinson´s disease (PD) is a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in the substantia nigra causing dopamine depletion in the striatum.However, the pathophysiological and compensatory mechanisms associated with the lesion are not well understood.The rat with a 6-hydroxydopamine (6-OHDA)-induced lesion in one hemisphere has been widely used as a model of PD. Dihydrotetrabenazine (2-hydroxy-3-isobutyl-9,10-dimethoxy-1,3,4,6,7-hexahydro-11bH-benzo[a]-quinolizine, 11C [DTBZ] has become the ideal radioligand for the presynaptic vesicular monoamine transporter VMAT2 based on its high binding affinity and optimal lipophilicity. The purpose of this study was to evaluated the effect that produce a longterm dopamine releasing device in caudate nucleus in hemiparkinsonism rat model on the motor alterations by behavioural tests and the density of dopaminergic receptors by Positron Emission Tomography. Material y Methods:For this study we worked with forty male Wistar rats divided in three groups: Group A) 8 control rats, Group B)12 injured rats by administration of the dopaminergic specific neurotoxin 6-OHDA (8microg/4microl) by stereoscopic surgery in the left median forebrain bundle, and Group C) 20 rats with the same lesion and the colocation of a dopamine continuous release implant made of titanium dioxide (TiO2DA). Twenty one days after the injury all the groups were undergo to the rotational-induced test with apomorphine (0.05 mg/kg, s.c) during fifty minutes in order to determine damage in dopaminergic system. Seventy five days after the injury a forced swim test and open field test were performed. Ninety days after the injury PET scans were obtained with the administration of carbon-11 labeled

dihydrotetrabezanine and the uptake of C11-DHTB was measured. One hundred and eighty days after the injury the rats was slaughtered. The uptake of the radiolabeled marker was compared with two-ways ANOVA with multiple comparison of Tukey test. Results: On PET the uptake of DTBZ in the right striatum measured with the Binding potential showed that the damage in the injured group who received the TiO2DA (Group C) had an uptake of the radio labeled marker lower (2619.91±503.89 nCi) than the injured animals without treatment (Group B: 7406.95±720 nCi), and that uptake was very similar to the control animals (Group A: 2650.00± 580.03 nCi).Spin test showed that the injured group spun more times (Group B: 401.5±44.16 spins) than the control group (Group A: 6+-2.44 spins) meanwhile group injured with implant (Group C: 44.25±16.71 spins). Forced swimming test we evaluated the locomotion, and we found that the animals with injury+TiO2DA moved more time (Group C: 47.75±5.365 s/min) in the pool than the just injured animals (Group B: 11.13±4.32 s/min) and was similar to the behaviour of the control animals in the test (Group A: 58±3.07 s/min). In the open field test we found the animals Injured + TiO2DA (Group C: displaced themselves more times (107.1±26.12 squares/5 min) than the injured animals (Group B: 10.5±5.52 squares/5min) and showed a behaviour similar to the control group (Group A: 136.1±5.35 squares/5min). Conclusion: With this results we can conclude that the application of the dopamine charged implant in the Caudate Nucleus achieved to decrease the motor alterations caused by the 6-OHDA. Meanwhile the animals which do not received the dopamine implant remained without changes in the motor function, and with an increased count of D2 dopamine presynaptic receptors.

23. **Acute stress in humans paradoxically enhances allocentric bias in a dual-strategy virtual Morris water maze. Mediation by sympathetic stress response?** Dustin van Gerven1, Ronald Skelton1. University of Victoria, Victoria, BC, Canada. In animal models, stress tends to impair hippocampal (HPC) function, especially in navigation tasks (Cazakoff et al., 2010). In humans, stress has produced mixed effects. Even in navigation tasks, stress has been found to facilitate, impair or have no effect on performance. The effects of stress on the HPC are proposed to be mediated by the actions of the HPA axis, via glucocorticoids, and the sympathetic-medullary-adrenal (SAM) axis. To date, only one study has examined the effects of stress on selection between two possible navigation strategies: an HPC-dependent allocentric strategy and a caudate-dependent egocentric strategy. This study found, as expected, that stress and cortisol impaired allocentric performance and biased the rats towards selecting an egocentric strategy. We sought to replicate this finding in humans. We used the PASAT (a difficult neuropsychological attention test) to induce stress and measured HPA and SAM activation. To assess HPC function, we tested navigation in a dual-strategy virtual Morris water maze that allowed participants to freely choose their navigational strategy and probed for strategy after every trial. To maximize the effect of HPA activation on the HPC, we tested navigation 20 minutes after the stressor (offset). In our participants (116 undergraduates, 58 males) the 10-min PASAT induced clear perceived stress (measured via STAI) and clear SAM activation (measured by HR, BP and skin conductance). However, SAM activation lasted less than 10 min and salivary cortisol measures in the stress group (n = 58) measured at the onset of navigational testing, were not significantly different from unstressed controls (p = .09). Surprisingly, the majority of stressed participants (64%) selected an allocentric strategy whereas unstressed controls tended to select an egocentric strategy (59%). Neither gender nor time of day (early vs later morning) was a factor in strategy selection. There were no significant differences in the navigational performance between stress and control groups, though stressed participants choosing allocentric navigation performed worse than those choosing egocentric navigation. Also surprisingly, there was no association between strategy selection and cortisol but there was a direct relation between strategy selection and SAM activation. These results indicate that in humans, HPC contributions to navigation may be more closely tied to SAM activation than HPA activation. Funding: NSERC scholarship to DVG.

24. **Akt signaling within the nucleus accumbens regulates functional reactivity to chronic social defeat stress in male mice.** Eric M. Parise1, Lyonna F. Alcantara1, Omar K. Sial1, Eric J. Nestler2, and Carlos A. Bolaños-Guzmán1**.** 1Department of Psychology and Program in Neuroscience, Florida

State University, Tallahassee, FL. 2Mount Sinai School of Medicine, New York, NY. Exposure to stress is a risk factor associated with the development of neuropsychiatric disorders. Unfortunately, the mechanisms that mediate the differential responses to stress are not well understood. Chronic social defeat stress (CSDS) is an ethologically relevant stress model capable of inducing core symptoms of depression and posttraumatic stress disorder that are measurable in rodents. The mesolimbic dopamine system, which includes the ventral tegmental area (VTA) and its projection regions, namely the nucleus accumbens (NAc), has received attention for its involvement in modulating responses to stress, as the VTA-NAc circuit plays a crucial role in integrating reward- and emotion-related behaviors. Akt signaling within the VTA regulates responses to stress; however, its role within the NAc is unknown. The present study was designed to assess the role of Akt-signaling within the NAc in modulating functional and biochemical responsivity to social defeat stress. Adult male mice were subjected to 10 days of CSDS followed by a social interaction test (SIT) 24 h after the last defeat. Mice were sacrificed either 24 h (short-term) or 1 month (long-term) after the SIT, and their brains were then processed for mRNA and protein changes in the NAc. Socially defeated mice show significant increases in Akt mRNA in both the short- and long-term conditions when compared to non-stressed controls. We observed increased phosphorylation of Akt protein after CSDS, but only in the long-term group, findings consistent with the enduring behavioral deficits observed in the SIT. This data suggests that Akt signaling within the NAc is significantly disrupted after CSDS exposure. To better understand the involvement of Akt in mediating stress-induced behavioral responding, we delivered herpes simplex virus (HSV) vectors overexpressing a constitutively active form of Akt (HSV-Aktca), a dominant negative inhibitor of Akt (HSV-Aktdn), or GFP (HSV-GFP) into the NAc and assessed functional reactivity to stress. Mice receiving HSV-Aktca into the NAc and then subjected to a sub-threshold defeat displayed significantly increased social avoidance. Conversely, inhibition of Akt, with HSV-Aktdn, in the NAc was sufficient to reverse the avoidant phenotype induced by 10 days of CSDS. These results suggest that Akt signaling within the NAc plays a crucial role in gating sensitivity to stress and may, in conjunction with changes in the VTA, mediate the depressive-phenotype induced by CSDS.

25. **The role of the cholinergic midbrain in sensory filtering and sensorimotor gating.** Azzopardi, E 1, & Schmid, S1. 1Department of Anatomy and Cell Biology, University of Western Ontario. Acetylcholine (ACh) is an important neurotransmitter that is involved in many aspects of cognition, but perhaps most notably in attention. Here, we aim to investigate the role of ACh in the preattentive processes of sensory filtering and sensorimotor gating. Sensory filtering is the removal of unnecessary sensory information from our conscious perception, freeing cognitive resources for more important information, whereas sensorimotor gating suppresses sensory evoked motor responses in favor of an orienting response towards a sensory stimulus. We study this using habituation and prepulse inhibition (PPI) of the acoustic startle reflex, respectively. Habituation is the exponential decrease in startle magnitude after repeated presentation of the startling stimulus and may occur within a testing session (short-term) or across days of testing (long-term). PPI occurs when the presentation of a prepulse inhibits the processing of the startling stimulus, resulting in a reduced startle magnitude. We used two transgenic mice with opposite perturbations in the cholinergic system to determine the role of ACh in habituation and PPI. A vesicular acetylcholine transporter knock down (VAChT KDHOM) mouse with a deficiency in cholinergic tone had normal short-term but impaired long-term habituation. They also displayed normal PPI, which was unexpected and contrary to previous studies in the field. A different transgenic mouseline had an overexpression of the cholinergic locus (B6.Cg-Tg(ChATCOP4*H134R/EYFP)6Gfng/J)-/+), giving them a hyperfunctioning cholinergic system. These mice had normal short and long-term habituation as well as PPI. As both our transgenic lines showed different roles for the cholinergic system in both PPI and habituation, our next step is to use a method less prone to developmental and compensatory confounding influences. To do this, we are using DREADDs to target the cholinergic midbrain center, the pedunculopontine tegmental nucleus (PPT). Currently, we are using a transgenic rat (Chat-Cre), and are injecting the PPT with a neuron silencer, AAV-hM4Di. Following infection, injection of the compound CNO will specifically silence cholinergic neurons of the PPT during sensory filtering tasks. This will allow us to further elucidate the role of the midbrain cholinergic system in habituation and PPI.

26. **The freely chosen tapping frequency of the index finger is increased over consecutive bouts of tapping.** Ernst Albin Hansen1,2, Jakob Rasmussen2, Brian Duborg Ebbesen2, Mark Holten Mora-Jensen2, Ane Dalsgaard2, Mahta Sardroodian1,2, Pascal Madeleine1,2. 1Center for Sensory-Motor Interaction (SMI), Aalborg University, Denmark, 2Deptartment of Health Science and Technology, Aalborg University, Denmark. Index finger tapping at freely chosen frequency can be considered a submaximal, rhythmic, and considerably simple and automated movement. Such movement has been suggested to be controlled by spinal neural networks assisted by descending drive and afferent feedback [1;2]. Force enhancement has been reported during submaximal voluntary contractions in finger muscles and suggested to possibly affect every day voluntary movements [3]. Yet, it is unknown if submaximal muscle activity also has an enhancing effect on temporal and spatial aspects of rhythmic finger movement. The present study first aimed to test if voluntary freely chosen index finger tapping frequency was increased in consecutive tapping bouts. Since that was confirmed, a follow-up experiment was performed to test if the increased tapping frequency was accompanied by kinetic (force) and kinematic (vertical displacement) changes. Healthy individuals took part in the first experiment (14 men, 8 women, 1.80±0.08 m, 77.6±12.0 kg, 24±3 years) and the follow-up experiment (11 men, 13 women, 1.74±0.09 m, 71.9±10.6 kg, 24±3 years). Unloaded, voluntary index finger tapping at freely chosen frequency was performed in bouts lasting 3 min each. Ten min rest separated the bouts. Four bouts were performed in the first experiment for measurement of tapping frequency. Two bouts were performed in the follow-up experiment for measurement of tapping frequency, force, and the index finger's vertical movement. In the first experiment, tapping frequency increased across bouts. Actually, a cumulating increase of the tapping frequency gradually amounted to a maximum magnitude of 8±5% ($p<0.001$) in the last bout compared to the first bout. This phenomenon is hereby suggested to be termed repeated bout rate enhancement. The follow-up experiment basically showed the same phenomenon as the tapping frequency increased by 6±11% ($p=0.035$) from 1st to 2nd bout. Though, the follow-up experiment showed no significant change in the peak tapping force from 1st to 2nd bout. Further, the increased tapping frequency was accompanied by a 6±15% decrease of the index finger's vertical displacement ($p=0.012$) during tapping. The latter suggests a trade-off between temporal and spatial characteristics of finger tapping in a state of repeated bout rate enhancement. References: 1. Zehr, Exerc Sport Sci Rev 33: 54-60, 2005. 2. Shima, et al., Conf Proc IEEE Eng Med Biol Soc: 4443-48, 2011. 3. Oskouei & Herzog, J Appl Physiol 98: 2087-95, 2005.

27. **Accelerated reading training improves reading fluency in Spanish speaking children. An eye-tracking study.** Gomez-VelazquezFabiola1 ; Gonzalez-GarridoAndres1,2; GarciaMonica1. 1University of Guadalajara, 2 Hospital Civil de Guadalajara. In languages with a consistent orthography, children with reading disabilities have a core deficit in reading speed; however, most training programs have focused on training in phonological skills, which are known to improve the efficiency but not reading speed. In this study we compare two short training programs in reading with emphasis on the processing of complex syllables and words using eye-tracking methods. In the first program children are encouraged to recognize rapidly syllables and word in isolation as well as within a text. In the second program the accelerated presentation of syllables, words and texts was used, forcing global recognition strategy, progressively increasing the rate of presentation of stimuli according to the child's abilities. Participants: 12 right-handed, Spanish speaking children between 9 and 10 years old participated in each training group. They all had reading disabilities according to standardized measures on reading speed and/or reading efficiency. A short narrative text was used to compare pre and post-training reading skills. The results showed a significant improvement in reading efficiency in both groups but only the group with accelerated reading training achieved a significant increase in reading speed. We also analyzed the number, position, and duration of fixations and the number and position of regressive saccades. While reading the text, the group that was trained with the accelerate strategy showed a significantly greater decrease in the duration of fixations, along with longer saccades. The present results reinforce the notion that the characteristics of the orthography of the language influence the strategies deployed to acquire automatic word recognition. Spanish-speaking children with reading difficulties have a marked difficulty in the use of strategies for automatic recognition of words, seeming to be more efficiently trained by using accelerated reading techniques.

28. **Influence of individual differences in impulsive action or impulsive choice on responding for a conditioned reinforcer and dopamine release.** F.D. Zeeb1, D. Funk2, A.D. Soko1, X. Ji1, P.J. Fletcher1,3. 1Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health (CAMH), Section of Biopsychology, Toronto ON, Canada, 2Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health (CAMH), Neurobiology of Alcohol Laboratory, Toronto ON, Canada, 3University of Toronto, Departments of Psychiatry and Psychology, Toronto ON, Canada. Clinical and pre-clinical studies suggest poor impulse control increases the risk of addiction and relapse. As exposure to drug-paired stimuli may contribute to relapse, trait levels of impulsivity may predict whether a conditioned stimulus acquires motivational salience and acts as a conditioned reinforcer (CR). The present study determined whether individual differences in two types of impulsive behaviour (action or choice) predicted the motivation to respond for a CR. In Experiment 1, rats were trained on the 5-choice serial reaction time task (5CSRTT), in which impulsive action was measured by the number of premature responses made prior to a cue. Rats were then separated into low (LI-A; n=9), intermediate (II-A; n=18), and high (HI-A; n=9) impulsive groups. In Experiment 2, rats were trained on the delay-discounting task to measure impulsive choice, which is defined as the selection of a small immediate reward over a larger delayed reward. Animals were then separated into low (LI-C; n=9), intermediate (II-C; n=8), and high (HI-C; n=13) groups. All rats were then tested on a CR paradigm, during which thirsty rats pressed a lever to receive a stimulus previously paired with water (a CR). The effects of an amphetamine (AMPH) injection were also assessed. In Experiment 1, AMPH increased impulsive action in all groups. Interestingly, LI-A rats initially responded more for the CR compared to both HI-A and II-A rats. Although AMPH increased responding for the CR in all groups, this effect was augmented in LI-A rats. As dopamine (DA) largely contributes to AMPH's effects on these tasks, in vivo microdialysis was used to measure DA release in the nucleus accumbens (NAc) in awake rats. The amount of DA released in response to an acute injection of AMPH was greater in LI-A rats. In Experiment 2, AMPH increased impulsive choice in the LI-C and II-C groups, but not the HI-C group. There were no group differences in the number of responses made for a CR and AMPH similarly increased responding for the CR in all impulsive choice groups. Likewise, the amount of DA released in the NAc following an injection of AMPH in LI-C and HI-C rats did not differ. In sum, these results suggest that there is no relationship between impulsive choice and responding for a conditioned reinforcer. However, HI-A subjects may have a hypofunctioning of DA within the NAc. This effect may contribute to the reduced reinforcing properties of a CR, especially in response to AMPH.

29. **Interplay between glutamatergic and cannabinoid systems within the dorsal periaqueductal gray matter modulates fear memory encoding and defensive behavior expression in an olfactory conditioning paradigm.** Back, F.P.1; Carobrez, A.P.1. 1Departamento de Farmacologia, CCB, Universidade Federal de Santa Catarina. 88048900 – Florianópolis, SC, Brazil. Classical conditioning paradigms offer controllable measurements for acquisition/encoding and expression of defensive coping strategies related to traumatic memories. In rodents, microinjections of N-Methyl-D-Aspartate (NMDA) into the dorsolateral portion of the periaqueductal gray matter (dlPAG) elicited defensive behavior (DB) as well as ascending negative valence instruction, serving as unconditioned stimulus (US), which supports fear encoding in conditioning paradigm. Since endocannabinoids are released on demand after neuron depolarization, and anandamide inhibits anxiety-like responses by activating type 1 (CB1) receptors within dlPAG, we proposed to investigate if CB1 receptors blockage would interfere with the CS-US association elicited from dlPAG NMDA activation. Wistar rats implanted with guide cannulas aimed at dlPAG were used throughout the experiments. The olfactory fear conditioning (OFC) protocol was performed during 5 consecutive days and composed of two stages: 1) conditioning (two days; Box A); and 2) expression (three days; Box B). In Experiment 1, twenty four hours after being familiarized in Box A, rats received microinjections (0.2 µl) of NMDA (25-50-100 pmol) and were replaced in the same box now saturated with amylacetate odor (CS). In Experiment 2, rats received microinjections of CB1 receptor antagonist, AM251 (50-100-200 pmol) followed by NMDA (25 pmol) and then were paired with CS. In both cases, OFC expression was performed in a Box B, during three days (familiarization, CS-exposure, Context-only exposure). DB was scored on days 2 (Box A) and 3, 4 and 5 (Box B). Experiment 1 showed that rats receiving 50 or 100 pmol expressed higher levels of DB than those treated with PBS or 25 pmol NMDA during CS

association. On the CS exposure, only rats from the 50 and 100 pmol groups were able to show an increased DB. In Experiment 2, the CB1 antagonist AM251 preceded sub effective (25 pmol) NMDA microinjection. CB1 receptor blockage was able to increase DB during the CS exposure when compared to AM251/PBS control. Therefore, the results confirm that NMDA into dlPAG can be used as US in classical conditioning paradigms. In addition, CB1 receptor antagonism potentiated the NMDA sub effective dose, suggesting interplay between glutamatergic and cannabinoid transmission in dlPAG on the modulation of DB. Altogether, the results suggest a dlPAG cannabinoid/glutamatergic balance during the processes of fear memory encoding and expression. Financial Support: CNPq; CAPES and FAPESP.

30. **Enhanced frontal cortex activity elicited by emotional stimuli in veterans with hazardous alcohol use and posttraumatic stress disorder.** Forster, Gina1,2, Olson, Dawne1,2, Baugh, Lee1,2, Hansen, Jamie3, Engel, Shaydel1,2, Simons, Raluca1,3, Simons, Jeffrey3, and Magnotta, Vincent4 1Center for Brain and Behavior Research, University of South Dakota, Vermillion, SD; 2Division of Basic Biomedical Sciences, Sanford School of Medicine, University of South Dakota, Vermillion, SD; 3Department of Psychology, University of South Dakota, Vermillion, SD; 4Depatment of Radiology, Carver School of Medicine, University of Iowa, Iowa City, IA. Many imaging studies suggest that posttraumatic stress disorder (PTSD) is associated with hypofunction of the anterior cingulate cortex (ACC), a finding thought to be related to poor inhibition of emotional states. For example, Vietnam veterans with PTSD fail to show rostral ACC activation during the emotional counting stroop task (ECST) in conditions when combat-related words are presented. However, other studies show increased activation of the ACC with combat-related imagery in veterans with PTSD. Differences between studies have been attributed to variation in the tasks used, the chronicity of PTSD, differences in PTSD symptomology, and regional differences in emotional processing within the ACC. Another factor that could influence frontal cortex function is alcohol use. As many as 50-85% of individuals with PTSD have a comorbid alcohol use disorder, and hazardous alcohol use is associated altered ACC activity. Therefore the current study aimed to determine behavioral and neural reactivity in response to the ECST in post-9/11 veterans with and without hazardous alcohol use. Eighty-five male and female right-handed veterans of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) were assessed for combat intensity, PTSD, and alcohol use and alcohol dependence. Participants underwent functional magnetic resonance imaging (fMRI) while performing the ECST adapted for OEF/OIF veterans. At the conclusion of scanning, participants provided arousal ratings for words comprising the ECST. Veterans with PTSD exhibited increased reaction times to combat-related words in the ECST, and provided higher arousal and negative ratings for combat words compared to veterans without PTSD. Interestingly, veterans with PTSD and hazardous alcohol use showed greater recruitment of rostral ACC and other frontal cortical areas in combat word conditions of the ECST as compared those with PTSD or hazardous alcohol alone. Overall, findings suggest that hazardous alcohol use might contribute altered rostral ACC reactivity in PTSD populations. Support: Department of Defense Research Grant (W81XWH-10-1-0925).

31. **Prenatal Stress and Acute Stress Later in Life Impacts The Responses in Tests for Depressive-Like Behavior in a Sex-Specific Manner.** Sickmann, Helle M.1,2,3; Skoven, Christian1; Arentzen, Tina S.1; Plath, Niels2; Bastlund, Jesper F.2; Dyrby, Tim B.3; Kohlmeier, Kristi A.1; Zhang Hui4; Kristensen. Morten P1. 1 Dept. Of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, DK-2100 Copenhagen, Denmark. 2 H. Lundbeck, Synaptic Transmission, DK-2500 Valby, Denmark. 3 Danish Research Centre for Magnetic Resonance, Hvidovre Hospital, DK-2650 Hvidovre, Denmark. 4 Department of Computer Science & Centre for Medical Image Computing, University College London, UK. Prenatal maternal stress increases the predisposition for affective disorders. Furthermore, women appear twice as likely as men to develop stress- and depression-related disorders. Comparable behavioral changes characteristic of clinical depression are found in rat offspring following prenatal stress (PS). These include increased helplessness, altered anxiety indicators and sleep modifications. Our purpose was to further investigate behavioral depression indices following PS as well as CNS structural changes including sex specificity of these variables. Pregnant Sprague-Dawley rats were exposed to repeated variable stress during days 13-21 of gestation. The PS paradigm consisted of two short-term stressors during the day (e.g. restraint and forced swimming) and a long-term stressor overnight (e.g.

fasting or lights on). We examined the rats at a young adult age for changes in locomotor activity, depressive- and anxiety-like behavior as well as sleep architecture. Some animals were analyzed for CNS microstructural changes based on diffusion MRI. Subsets of PS and control rats were exposed to an acute stressor prior to the behavioral tests. Rearing/climbing activity in a familiar environment (housing cage) increased at the end of the light and beginning of the dark phases in PS offspring compared to controls. PS per se did not appear to change anxiety-like behavior in either sex. However, exposure to an acute stressor increased exploratory behavior in control animals and, interestingly, PS blunted this effect. Relative and absolute numbers of rapid eye movement sleep bouts were higher in PS offspring. Moreover, exposure to an acute stressor induced a REM rebound effect in control animals but this compensatory mechanism was blunted in PS animals. Finally, depression-like behavioral changes assessed in the forced swim test was selectively induced in PS females. The central mechanisms mediating these differences may contribute to sex-specific sensitivity to stressors and depression propensity in humans. We would like to acknowledge The Danish Innovation Foundation and The Lundbeck Foundation for funding the studies.

32. **Characterization of ketamine and selective NR2B antagonists in animal models predictive of antidepressant activity.** Shoblock, James1; Welty, Natalie1; Lord, Brian1; Azar, Marc2; Willems, Roland3; Ver Donck, Luc3; Bonaventure, Pascal1; Lovenberg, Tim1; Balana, Bartosz1; Chen, Guang1. 1Neuroscience, Janssen Research & Development. San Diego, CA 92121 USA, 2Behavioral Pharma, Inc. 505 Coast Blvd. South, Suite 212 La Jolla, CA 92037 USA, 3Neuroscience, Janssen Research & Development. Turnhoutseweg 30 B-2340, Beerse Belgium. Ketamine, a non-selective open channel blocker at NMDA channels, as well as more selective drugs targeting NMDA channels containing NR2B subunits, have been used clinically for depression. The aim of the present study was to characterize NR2B antagonists in animal models related to depression and to compare to ketamine in terms of side-effects and mechanism of action. Ketamine and the NR2B antagonist CP-101,606 (Traxoprodil) both decreased immobility time in the tail suspension test, a model highly predictive of antidepressant-like activity. While CP-101,606 had no effects on locomotor activity, ketamine produced an inverted-U shaped dose response effect on locomotor activity. Ex vivo receptor occupancy revealed that the NR2B antagonist needed ~80% receptor occupancy at NR2B for substantial effects in tail suspension while ketamine occupied a significantly lower proportion of its pore binding site. Next, antagonists at various different receptors were pretreated before ketamine or CP-101,606 injection and tested in tail suspension to determine if the mechanism of action between ketamine and CP-101,606 was similar. The effect of ketamine was significantly attenuated by NBQX, an AMPA receptor antagonist, or a sigma-1 receptor antagonist, whereas these pretreatments did not affect the efficacy of CP-101,606. Pretreatment with a dopamine D1 receptor antagonist had no clear effects. A D2/D3 receptor antagonist attenuated the effect of both CP-101,606 and ketamine, but also increased immobility on its own and caused hypoactivity. Interestingly, CP-101,606, but not ketamine, was able to block the pro-depressant-like effect of the D2/D3 antagonist, and did not affect the hypoactivity caused by the D2/D3 antagonist. In follow up studies of side-effects, it was shown that both ketamine and CP-101,606 disrupted prepulse inhibition, without affecting startle response, however, the effect of CP-101,606 was more mild. In addition, while relatively high doses of ketamine sustained self-administration in rats, CP-101,606 produced lever pressing rates comparable to saline at the doses tested. These studies show that both NMDA antagonists and selective NR2B antagonists are active in models predictive of antidepressant activity, however, the side-effect profile of ketamine may be more pronounced than NR2B antagonists and the mechanism of action may differ, perhaps with ketamine, but not CP-101,606, involving an AMPA-mediated disinhibition of cortical networks.

33. **Fluoxetine exposure during adolescence disrupts spatial memory performance in adulthood.** Jason B. Alipio, Bryan Cruz, Kristi L. Shawhan, Lace M. Riggs, & Sergio D. Iñiguez**.** Department of Psychology, California State University, San Bernardino, CA 92407**.** Epidemiological reports indicate that mood-related disorders are common in children and adolescents. The prevalence of adolescent depression has resulted in parallel increases in the prescription of fluoxetine (FLX, Prozac), the only antidepressant currently approved by the FDA for treatment within this population. Although treatment can last for years, very little is known about the long-term consequences of antidepressant exposure during early developmental periods prior to adulthood on memory performance later in life. Thus, we

exposed adolescent (postnatal day [PD]-35) and adult (PD65) male c57BL/6 mice to FLX (0 or 20 mg/kg) for 15 consecutive days. We then assessed animals' behavioral performance on the Morris Water Maze spatial memory task, three weeks after antidepressant exposure. Specifically, mice were trained to find the location of a submerged escape platform on a single day task of 8 training trials, and memory for the platform location was re-tested after a 24 hour delay (distance traveled and velocity). To increase the demands of the spatial task, the mice returned to the spatial task, 48 hours after training, and completed a probe trial (escape platform absent), and the total time spent in the quadrant of the target platform location was recorded. We found that FLX exposure, regardless of age, did not influence spatial memory acquisition on the training day. In addition, no differences between the groups were observed when spatial memory was examined 24 hours after training. On the other hand, mice exposed to FLX during adolescence, but not adulthood, spent significantly less time in the target quadrant when tested 48 hours after training (probe trial). Together, our results suggest that as the demands of the spatial memory task increase, spatial memory deficiencies become apparent in adult mice exposed to FLX during adolescence. This highlights the need to further investigate enduring consequences associated with adolescent exposure to FLX treatment.

34. **Role of projections from ventral subiculum to nucleus accumbens shell and ventral medial prefrontal cortex in context-induced reinstatement of heroin seeking.** Bossert JM1, Adhikary S1, St. Laurent RM1, Marchant NJ1,3, Wang HL2, Morales M2, and Shaham Y1. 1Behavioral Neuroscience Branch, 2Integrative Neuroscience Branch, IRP/NIDA/NIH/DHHS, 3Florey Institute of Neuroscience & Mental Health, University of Melbourne, Parkville, VIC, Australia**.** Background: In humans, exposure to contexts previously associated with heroin use can provoke relapse. In rats, exposure to heroin-paired contexts after extinction of drug-reinforced responding in different contexts reinstates heroin seeking. We previously demonstrated a causal role for projections from ventral medial prefrontal cortex (mPFC) to accumbens shell in this reinstatement. Because ventral subiculum also sends glutamate projections to accumbens shell, as well as ventral mPFC, we sought to determine whether these projections also contribute to context-induced reinstatement. We first combined Fos with the retrograde tracer Fluoro-Gold to assess whether these pathways are activated during context-induced reinstatement. We then employed an anatomical disconnection procedure to determine whether these projections are functionally involved in this reinstatement. Methods: We trained rats to self-administer heroin for 12 days; drug infusions were paired with a discrete tone-light cue. Lever pressing was subsequently extinguished in a non-drug-associated context in the presence of the discrete cue. We then tested the rats in the heroin- and/or extinction-associated contexts under extinction conditions. Results: Exposure to the heroin but not extinction context reinstated lever pressing. Context-induced reinstatement was associated with increased Fos expression in ventral subiculum neurons, including those projecting to accumbens shell or ventral mPFC. We also found that inactivation of ventral subiculum in one hemisphere combined with dopamine D1 receptor blockade into contralateral or ipsilateral accumbens shell decreased this reinstatement. Conclusions: Results suggest that the glutamatergic projections from ventral subiculum to accumbens shell are part of a circuit in which activation provokes context-induced relapse to heroin seeking. We are currently testing whether disconnection of the ventral subiculum → ventral mPFC pathway will also decrease this reinstatement. Financial support provided by IRP/NIDA/NIH.

35. The role of behavioral flexibility in anxiety vulnerability. Jennifer E. Catuzzi Fragale 1,2, Kevin D. Beck1,2, and Kevin C.H. Pang1,2. 1Neurobehavioral Research Laboratory, Research Service, VA New Jersey Heath Care System, East Orange, NJ 07018, USA**.** 2Graduate School of Biomedical Sciences, New Jersey Medical School, Rutgers, The State University of New Jersey, Newark, NJ 07103, USA. Behavioral flexibility refers to one's capacity to adapt learned behaviors to accommodate unexpected changes in the environment. Flexible learning is dependent on activation of the ventromedial prefrontal cortex (vmPFC) and several neuropsychiatric disorders associated with vmPFC dysfunction exhibit a lack of behavioral flexibility. Anxiety disorders are among the group of neuropsychiatric disorders associated with vmPFC dysfunction and inflexible behaviors. One of the most striking examples of inflexible learning in anxiety disorders is the presence of pathological avoidance. However, studies investigating the role of behavioral flexibility in anxiety disorders have provided inconsistent findings. In the present study, we sought to determine if inflexible rule learning represents an anxiety vulnerability factor. Using a model of anxiety vulnerability, the Wistar Kyoto

(WKY) Rat, we sought to address this question. WKY rats naturally exhibit inflexible learning in the form of extinction resistant avoidance and exhibit an innate lack of NMDA-dependent long-term potentiation in a sub-region of the vmPFC. Thus, we hypothesized that anxiety vulnerable WKY rats would naturally lack behavioral flexibility. Anxiety vulnerable WKY and non-vulnerable Sprague Dawley (SD) rats were tested in a maze-based set shifting task. In this task rats were presented with two stimulus domains (color and texture) with only one domain predictive of reinforcement. Once the initial rule was acquired the reinforced domain was switched to the previously irrelevant domain. Our results show that WKY rats acquired initial rule learning faster than SD rats. Surprising, WKY rats also acquired extradimensional shifts faster than SD rats. This result was associated with a significant decreased in perseverative errors by WKY rats. While on the surface it appears that WKY rats show greater behavioral flexibility, these results may actually stem from a lack of proactive interference observed in anxiety vulnerable individuals. These results provide insight into the development of anxiety disorders, as anxiety vulnerable individuals may learn stimulus associations separately and be unable to integrate information to adapt behavior. Funding: The research presented in the current study was funded by the Biomedical Laboratory Research and Department of Veterans Affairs Office of Research & Development (1I01BX000218 and I01BX000132), the NIH (RO1-NS44373).

36. **The rapid effects of medial amygdalar and hippocampal G-protein coupled estrogen receptor on social recognition learning in female mice.** Jennifer Lymer1, Andrea Blackman1, Cassandra Barrett1, and Elena Choleris1. 1Psychology and Neuroscience Program, University of Guelph, Guelph, Canada. Estrogens have been found to rapidly affect learning and memory in various tasks, including that of social recognition (Phan et al., 2011, 2012). These effects occur within 40min of drug administration and can be elicited through the three main estrogen receptors (ER), ERα, β, and the G-protein coupled estrogen receptor (GPER). When agonists for ERα or the GPER are administered systemically to ovariectomized female mice immediately before the learning task, the mice show improvements in social recognition. Conversely, when an ERβ agonist is administered, the mice show impairments in social recognition (rev. in Gabor et al., 2012). The next step was to determine which ERs in which brain regions might be involved in mediating these rapid improvements. Two brain regions of interest are the hippocampus, which has been shown to mediate estrogenic improvements on social recognition through ERα, and the medial amygdala, which has been shown to be necessary for social recognition (Wang et al., 2014). Evidence has also shown that estrogens in the medial amygdala, specifically through ERα, play a necessary role in social recognition (Spiteri et al., 2010). The involvement of the GPER in the hippocampus and medial amygdala is currently unknown. The present study investigated the effects of the of the GPER agonist, G-1 (25, 50, 100, 200, 300, 400nM; 0.5μL at rate: 0.2μL/min) in the hippocampus and medial amygdala on social recognition. G-1 was infused directly into the target brain region of ovariectomized female mice 15min before the social recognition paradigm. The paradigm was 25min, consisting of two 5min habituations and one 5min test phase, with 5min inter-trial intervals. The paradigms end 40 min post-infusion, allowing for the investigation of the rapid effects of estrogens. Two conspecific stimulus mice were presented in the habituations, with one of the stimuli replaced by a novel stimulus mouse in the test phase. Social recognition was improved with hippocampal infusion of 50nM and 200nM G-1. Preliminary results suggest that medial amygdalar infusion of 50nM G-1 also improves social recognition. Therefore, activation of the GPER specifically in the hippocampus or medial amygdala can facilitate social recognition learning. Thus, estrogens in the hippocampus or medial amygdala may be able to mediate social recognition learning through the GPER. Supported by NSERC.

37. **Lack of depression-like phenotypes in C57BL-6J mice subjected to different types of chronic stressors.** Jillian R. Hufgard1, Michael T. Williams2, and Charles V. Vorhees2. 1 Department of Pediatrics, College of Medicine, University of Cincinnati 2 Division of Neurology, Cincinnati Children's Research Foundation. Depression is the number one cause of suicide and the fourth leading cause of disability in the United States. Despite the 298 million people worldwide affected by depression, we have very little knowledge on the etiology, prevention, or cure for depression. Many different animal models have been used to research both acute and chronic stressors as a means of exploring depression. We tested four different methods of chronic stress to induce depression in C57BL/6J male mice. Depression-like phenotype was examined following each of the stressors with tail suspension test (TST), forced swim test (FST), and sucrose preference test (SPT) and body weights

and corticosterone were measured during and following each chronic stressor. At the end of testing weights of the spleen, adrenal glands, and thymus were measured. We tested three different protocols of chronic variable stress that spanned 14-21 days of stress and included both physiological and psychological stressors; we also tested 21 days of restraint stress in shallow water. Each of the four stress protocols produced an increase in corticosterone in the stressed mice compared with the non-stressed mice, during the stress paradigm and after the completion of all behavioral testing. There was also a decrease in weight gain in the stressed group over time compared with non-stressed mice. After the completion of the chronic restraint stress in shallow water there was no difference in FST, TST, SPT, or organ weights between the two groups. The first version of CVS (stressed for 14 days with psychological stressors) showed no difference in FST, TST, or organ weight, but there was a significant difference in SPT (Control: 92.9+/-1.49% n=8 Stress: 52.07+/-20.05% p≤0.02). The second version of CVS used tested acute stress, 14 days of stress, and 21 days of stress; with this version we found an increase in time spent immobile for the 21 day stress group, a decrease in SPT for the 14 day stress group, and a decrease in percentage of thymus to body weight for both the 14 and 21 day stress groups. For the fourth method of CVS we added the physiological stressors of hypoxia and cold room exposure and there was no change in FST or TST, although there was a decrease in percentage of thymus to body weight of the stress group indicating the animals were stressed (Control: 0.13+/-0.005% n=11 Stress: 0.06+/-0.007% n=11 p≤0.001). None of the stress paradigms produced a consistent and lasting depression-like phenotype despite the similarity of the stress paradigms to published protocols.

38. **Inhibiting lactation increases depression-like behavior in postpartum rats.** Joanna L. Workman1,2, Aarthi R. Gobinath2, Sophia Solomon2, Carmen Chow2, and Liisa A.M. Galea2**.** 1University at Albany, State University of New York**.** 2University of British Columbia**.** Women are at least twice as likely as men to develop depression and the postpartum period represents a particular time of risk. Approximately 15% of women develop postpartum depression (PPD) and of those women, a significant number also discontinue breastfeeding. It is unclear, however, whether discontinuation of breastfeeding increases the risk for PPD. We hypothesized that surgical blockade of milk letdown (which in turn, inhibits lactation) in a rat model would increase depression-like behavior as measured in the forced swim test (FST; a commonly-used and well-validated behavioral test that approximates symptoms of depression). Adult female rats received either thelectomy (surgical removal of teats) or sham surgery and 7 days later, all females were mated with males. Upon parturition, litters were culled to 8 pups and pups were rotated to shams every 12 hours to ensure adequate milk intake. Thus, pup exposure to thelectomized (Thel) females was yoked to that of paired sham females. Maternal behaviors were scored during the first week of the postpartum period. Thel females spent less time self grooming and nest building than sham females but spent slightly more time in contact with pups. All females were then tested in an open field and FST 3 times throughout the postpartum period. Thel females spent more time immobile in the FST at the end of the postpartum period and traveled a greater distance in the open field mid-postpartum. Collectively, these data suggest that inhibiting lactation increases depression-like behavior independently of motor activity and pup contact. Thel females also had greater uterine mass (even when controlled for body mass) and had an earlier onset of estrus. Brains are currently being evaluated for spine density and dendritic complexity in the hippocampus and prefrontal cortex. This research will be instrumental in understanding emotional and neural changes that occur in women who discontinue breastfeeding early postpartum. This research was supported by a NARSAD Young Investigator Award from the Brain and Behavior Research Foundation to JLW.

39. **The long-term, sex-dependent effects of adolescent social stress on depressive-like behavior and stress-related neurocircuitry.** Lukkes, Jodi L.; Norman, Kevin J.; Meda, Shirisha; Andersen, Susan L.; McLean Hospital and Harvard Medical School, Belmont, MA, USA. Exposure to adverse experiences during adolescence increases vulnerability to stress-related neuropsychiatric disorders of depression and anxiety during adulthood. Few preclinical studies have examined the sex-dependent effects of adolescent isolation-rearing on depressive-like behavior in adulthood, resulting in a poor understanding of the underlying mechanisms. Our previous studies have shown that adolescent isolation-rearing in male rats up-regulates corticotropin-releasing factor (CRF) type 2 receptors in the dorsal raphe nucleus (DR), prolongs CRF-mediated serotonin release in the nucleus accumbens, and

increases social anxiety-like behavior in adulthood that can be attenuated with antagonism of CRF receptors in the DR. We hypothesize that isolation-rearing sensitizes a stress-related serotonergic pathway in the DR in a sex-dependent way that increases vulnerability to develop anxiety- and depressive-like behavior in adulthood. Therefore, we examined the long-term effects of isolation-rearing during adolescence on adult anxiety-like behavior using the elevated plus maze and depressive-like behavior using the learned helplessness triad (LH; escapable shock (ES), inescapable shock (IS), and no shock (NS) groups) in both male and female rats. The LH triad allows an in-depth characterization of multiple aspects of depressive-like behavior as each condition is mediated partly by separate neuronal circuits. Utilizing qRT-PCR, we also examined isolation-induced changes in CRF1 and CRF2 receptor mRNA expression in five subregions of the DR that have specific projections to stress-related forebrain regions. Adolescent isolation-rearing in both males and females increased anxiety-like behavior. Increased depressive-like behavior following adolescent isolation-rearing was observed in ES and NS males only, suggesting controllability and motivational deficits. This sex-dependent effect of isolation-rearing on depressive-like behavior indicates that perhaps a different type of social experience during adolescence is needed to induce depressive-like behavior in females. Isolation-rearing of males decreased CRF2 receptor mRNA expression, whereas group-rearing increased CRF1 receptor mRNA expression in the dorsal part of the DR. This region projects to several anxiety- and depression- related pathways, such as the medial prefrontal cortex and nucleus accumbens. These data suggest that adolescent isolation-rearing has sex-dependent, long-term effects on behavior and stress-related serotonergic systems that are implicated in the pathophysiology of neuropsychiatric disorders, such as depression and anxiety.

40. **Effect of chronic stress on markers of plasticity associated with mPFC mediated cognitive flexibility in rats.** Julianne D. Jett, Lauren Evans, and David A. Morilak**.** Department of Pharmacology and Center for Biomedical Neuroscience University of Texas Health Science Center at San Antonio. Deficits in cognitive flexibility are associated with the onset and maintenance of stress-related neuropsychiatric disorders, such as depression. Cognitive flexibility, the ability to modify behaviors in response to changes in the environment, is mediated by medial prefrontal cortical (mPFC) function. Previously, we showed that chronic unpredictable stress (CUS) induced impairments of cognitive flexibility specific to mPFC function in rats, as assessed by the extra-dimensional set-shifting task (ED) of the attentional set-shifting test. This CUS-induced impairment in cognitive flexibility was associated with an attenuated c-fos response in the mPFC following pharmacological activation of the mediodorsal thalamus (MDT), a glutamatergic afferent of the mPFC. Moreover, our subsequent studies found that inducing long-term potentiation in the mPFC by applying high frequency stimulation in the ventral hippocampus (vHipp), also a glutamatergic afferent of the mPFC, reversed CUS-induced cognitive deficits on ED. Thus, deficits in cognitive flexibility may result from CUS compromising glutamatergic afferents to the mPFC and/or markers of plasticity in this region. To test this hypothesis, we first investigated the effects of CUS on mPFC response to MTD or vHipp stimulation using electrophysiological techniques. Male Sprague-Dawley rats were exposed two 2 weeks of non-stressed handling conditions or CUS. The day after the last stress treatment, rats were anesthetized and a stimulating electrode placed in the MDT or vHipp, along with a recording electrode in the mPFC. A current response curve was then established by recording field potentials in the mPFC after single pulse stimulation of the MDT or vHipp. Our results indicate that CUS attenuates mPFC response to MDT stimulation compared to non-stressed controls ($p<0.005$, $n = 4$-5/group). In contrast, the present study found no difference between non-stress and CUS conditions in mPFC response to vHipp stimulation ($p>0.8$, $n = 5$-6/group). The lack of CUS effect on mPFC response to vHipp stimulation suggests that plasticity in different afferent pathways may be involved in the onset of stress-induced cognitive impairment, i.e. MDT, and the restoration of cognitive function with effective therapies, i.e. vHipp. Studies are ongoing to assess if CUS compromises molecular markers in the mPFC associated with long-term potentiation (i.e., PSD-95, activity-regulated cytoskeleton-associated protein, AMPA and NMDA receptor subunit phosphorylation), both at baseline-cage control conditions and following completion of the extra-dimensional set-shifting task of AST. By elucidating the mechanisms that link chronic stress to mPFC dysregulation and cognitive dysfunction, these findings may contribute to the development of novel, more effective, therapies for the treatment and prevention of stress-related mental illnesses.

41. **Stress affects response inhibition when emotional contexts are involved.** Ramos-Loyo, Julieta, Briseño-Pulido, José Eduardo. Institute of Neuroscience, University of Guadalajara, Mexico. The objective of the present study was to identify whether the stress conditions experienced by students at the end of an academic period have a deleterious effect on response inhibition processes when emotional contexts were present, evaluated both at the behavioral and electrophysiological level (PREs). Adult posgraduate students participated in the study, who were evaluated in 2 sessions in a counterbalanced way: with low stress level at the beginning of the academic semester and, under stress at the end of the semester. A Go/NoGo task was applied under 4 conditions: without context and, with neutral, pleasant and unpleasant contexts. Subjects presented lower number of correct inhibitions in the unpleasant context under stress. As well, P3 amplitude in parietal leads and late positive potential (LPP) amplitude in prefrontal leads were also higher in the unpleasant context under stress in the NoGo trials. Present results suggest that when students are under stress, they require higher neural resources in order to inhibit a prepotent response when unpleasant emotional contexts are present. This may be due to the fact that stress induces higher limbic activation, therefore cortical control is not efficient enough to undergo response inhibition.

42. **Changes in serotonin signaling alter multisensory function in the mouse: Implications for autism.** Justin K. Siemann1, Christopher L. Muller1, Gunnar C. Forsberg1, Randy D. Blakely1, Jeremy Veenstra-VanderWeele2 and Mark T. Wallace1. 1Vanderbilt University, 2Columbia University. Autism spectrum disorders (ASD) are complex neurodevelopmental disorders characterized by the presence of repetitive/restrictive behaviors and impairments in both communication and social behaviors. In addition, sensory disturbances have been consistently observed, with growing evidence that these impairments extend to processing multisensory information. The goal of this study was to evaluate basic aspects of sensory and multisensory processing in a mouse model that displays many of the phenotypic characteristics of ASD. A rare variant in the serotonin transporter (SERT) has been associated with autism in the human population, and mice expressing this variant exhibit changes in domains such as social interactions, communication and repetitive behaviors. In this study, mice were first trained to respond to auditory and visual stimuli independently. Animals were then tested under visual, auditory or paired audiovisual stimuli to determine the benefit of congruent multisensory stimuli on behavioral performance. A variety of stimulus durations were tested to determine the effects on multisensory processing. Wild type mice exhibited significant gains in response accuracy under multisensory conditions, with the largest gains observed for stimuli presented at 500 ms and 300 ms durations. However, SERT variant animals failed to exhibit behavioral gains under multisensory conditions, despite being able to learn the auditory and visual tasks in an equivalent manner to wild type animals. Therefore, the results represent the first behavioral study to demonstrate and evaluate atypical multisensory processing in a mouse model that displays a number of behavioral phenotypes associated with autism. This work was supported by Vanderbilt University Institutional Funding and 5T32MH018921-24: Development of Psychopathology: From Brain and Behavioral Science to Intervention. This work was performed in part through the use of the Murine Neurobehavior Core lab at the Vanderbilt University Medical Center, which is supported in part by P30HD1505.

43. **The role of endogenous nociceptin in anxiety-like behaviors in C57/BL6 mice.** 1Perez, Sidney; Marquez, Paul2; Hamid, Abdul2; Lutfy, Kabirullah2**.** 1California State Polytechnic University, Pomona, California, USA; 2College of Pharmacy, Western University of Health Sciences, Pomona, California, USA. Orphanin FQ/nociceptin, the endogenous ligand of the opioid receptor-like (ORL1, also known as NOP) receptor, has been shown to regulate anxiety-like behaviors in rodents. Low doses of the peptide reduce anxiety but higher doses of nociceptin are found to be pro-anxiety. However, the role of endogenous nociceptin in this process is not fully characterized. Importantly, the role of gender in this process is not known. Thus, the goal of the present study was to assess the role of endogenous nociceptin in anxiety-like behaviors and to determine whether there is a gender-related difference in this response. Mice lacking the prepro-orphanin FQ/prepro-nociceptin gene and their wild-type controls have been generated which represent an ideal model to address these research questions. Thus, using male and female mice of these mice and their wild-type littermates/controls and the elevated plus maze, which is widely used as an animal model of anxiety-like behaviors, we sought to

characterize the role of endogenous nociceptin in anxiety-like behaviors. Male and female mice of each genotype were bought to the laboratory and allowed to habituate to the testing room for 1 h. Mice were then tested on the EPM for 5 min, in which each mouse was placed on the elevated plus maze and the amount of time that each mouse remained in the open arms was calculated and compared to their respective wild-type control. Our results showed that older male mice lacking the prepro-nociceptin gene spent significantly lesser amount of time on the open arms compared to their wild-type littermates/controls, showing greater anxiety-like behaviors in these mice. However, this difference was not present between younger male mice of the two genotypes. Furthermore, there was no difference between female mice of the two genotypes at any age. Together, these results suggest that the endogenous nociceptin system may serve a protective role against the development of anxiety in older mice and there exists a gender related difference in this process.

44. **Prenatal nicotine exposure impairs the proliferation of neuronal progenitors, leading to fewer glutamatergic neurons in the medial prefrontal cortex.** 1Yamada, Kiyofumi; 1,2Aoyama, Yuki; 2Toriumi, Kazuya; 2Mouri, Akihiro; 2Mamiya, Takayoshi; 1Nagai, Taku; 3Kim, Hyoung-Chun; 2Hiramatsu, Masayuki; 2,4Nabeshima, Toshitaka. 1Dept Neuropsychopharmacol Hosp Pharmacy, Nagoya Uni Grad Sch Med, Japan, 2Dept Chem Pharmacol, Fac Pharm, Meijo Uni, Japan, 3Dept Neuropsychopharmacol Toxicol Program, Col Pharmacy, Kangwon Nation Uni, South Korea, 4Dept Region Pharm Care Sci, Fac Pharm, Meijo Uni, Japan. Cigarette smoking during pregnancy is associated with various disabilities in the offspring such as AD/HD, learning disabilities, and persistent anxiety. We have reported that nicotine exposure in female mice during pregnancy, in particular from E14 to P0, induces long-lasting behavioral deficits in offspring. However, the mechanism by which prenatal nicotine exposure (PNE) affects neurodevelopment, resulting in behavioral deficits, has remained unclear. Here, we report that PNE disrupted the proliferation of neuronal progenitors, leading to a decrease in the progenitor pool in the ventricular and subventricular zones. In addition, using a cumulative BrdU labeling assay, we uncovered anomalous cell cycle kinetics in mice with PNE. Accordingly, the density of glutamatergic neurons in the medial PFC was reduced, implying glutamatergic dysregulation. Mice with PNE exhibited behavioral impairments in attentional function and behavioral flexibility in adulthood, and the deficits were ameliorated by microinjection of D-cycloserine into the PFC. Collectively, our findings suggest that PNE affects the proliferation and maturation of progenitor cells to glutamatergic neuron during neurodevelopment in the medial PFC, which may be associated with cognitive deficits in the offspring. Supported by Grants-in-Aids for Scientific Research from JSPS; by the “Academic Frontier” Project for Private Universities (2007–2011) from MEXT; by the “Integrated Research on Neuropsychiatric Disorders” and “Bioinformatics for Brain Sciences” carried out under the SRPBS from MEXT; by the Research on Regulatory Science of Pharmaceuticals and Medical Devices from the Ministry of Health and Labour Sciences from MHLW; by a grant from the joint research project under the Japan-Korea basic scientific cooperation program (JSPS); by a Research Grant from the SRF.

45. **Broadband local field potential characteristics in rat cingulate cortex are predictive of high-effort, goal-directed behaviour.** Kristin Hillman and David Bilkey. University of Otago, Department of Psychology, Dunedin, New Zealand. Converging work on the anterior cingulate cortex (ACC) suggests that this region plays a critical role in motivating goal-directed behaviours, particularly by biasing actions towards goals that present optimal effort:outcome payouts. ACC activity may therefore help prompt an individual to invest effort towards a goal, when the outcome is worth that effort. However it is not known whether small but significant variations in basal ACC activity predict individual variations in effortful goal-directed behaviour. Here we tested the hypothesis that ‘high effort’ and ‘low effort’ laboratory rats could be delineated prior to actual effort:outcome testing tasks, based on broadband ACC local field potential (LFP) characteristics. Sprague Dawley rats (n=6) were chronically implanted with adjustable electrode arrays in ACC; bandpass filtered LFP activity is presented here. Each recording session consisted of an initial open field assessment, followed by one of three tasks: an effortful persistence task, a cost-benefit decision-making task, or an open field foraging task. Power spectral density analysis of ACC LFPs revealed significant power differences

between ‘high effort’ and ‘low effort’ rats over multiple frequency bands both during the tasks, and during initial open field assessments. These preliminary findings suggest that ‘high effort’ individuals can be identified via broadband LFP characteristics in ACC, prior to actual observed high-effort goal-directed behaviour. This work was supported by a Marsden Fast Start Grant from the Royal Society of New Zealand.

46. **The effect of MMP-9 manipulation on social behavior.** Meyza Ksenia1, Kondrakiewicz Kacper1, Ziegart-Sadowska Karolina1, Nikołajew Tomasz1, Puścian Alicja1, Knapska Ewelina1**.** 1. Laboratory of Emotions’ Neurobiology. Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland. Matrix metallproteinase-9 (MMP-9) activity in the central nucleus of the amygdala has been previously implicated in modulation of appetitive learning in mice (Knapska et al. 2013). Since social interaction has rewarding properties (Pearson et al. 2012, Martin et al. 2014), the aim of our study was to investigate the effects of increase of MMP-9 expression in the CeA on social motivation. We have used two models of MMP9 overexpression: a transgenic mouse and a local overexpression of MMP9 by a lentiviral vector. The mice were tested in the social approach test (using the 3 chambered apparatus). Our results indicate that local elevation of MMP-9 level in the CeA increases motivation for exploration, but the social aspect of it is less affected. The general overexpression results in a milder phenotype. These results underline the role of MMP-9 in the CeA in forming of motivational drives in mice.

47. **The TNF- antagonist Enbrel produces reversals in forced-swim test and object memory deficits induced by repeated corticosterone administration in rodents.** Kyle Brymer1, Hector J Caruncho2, & Lisa E. Kalynchuk3**.** 1Department of Psychology, University of Saskatchewan, Saskatoon, Saskatchewan**.** 2College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan**.** 3Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan**.** Exposure to stressors frequently precedes the onset of depression in human patients. Accordingly, many preclinical rodent models of depression make use of chronic exposure to stress or glucocorticoids to induce a depressive phenotype. Furthermore, chronic exposure to stress promotes the release of cytokines, which in turn exacerbate the stress response and disrupt cognition. Prominent among these is the cytokine TNF-alpha, which is preferentially expressed in the hippocampus and pre-frontal cortex. Following this, we hypothesized that exposing rodents to repeated stress will up regulate TNF-alpha within the hippocampus and pre-frontal cortex, and disrupt behavioral tasks dependent on those areas. Therefore, treating chronically stressed rats with drugs that block the action of TNF-alpha should ameliorate behavioral task deficits. In this experiment, we examined the effect of repeated corticosterone (CORT) treatment and concurrent TNF-alpha antagonism (Enbrel) on cross-modal memory and forced-swim test memory (FST). Additionally, we examined object-location and object-in-place memory, tasks dependent on the hippocampus and pre-frontal cortex, respectively. Previous work in our lab has demonstrated that repeated CORT injections induce deficits in both object-location and object-in-place memory, however no research has examined CORT’s effects on cross-modal memory. Rats received either 21 days of daily CORT injections (40 mg/kg) or vehicle injections, in addition to semi-weekly injections of Enbrel (0.8 mg/kg) or vehicle, with behavioral testing commencing on day 22. Reduced immobility time in the FST was observed in CORT alone rats, and was reversed in CORT Enbrel rats. Interestingly, CORT alone rats were significantly impaired on both object-location and object-in-place memory, and treatment with Enbrel reversed both of these memory deficits. Lastly, a trend emerged whereby CORT alone rats were impaired on cross-modal memory, and treatment with Enbrel brought performance back to control levels. These results confirm that impaired object-location and object-in-place memory are part of the depressive phenotype seen in CORT alone rats. However, these are the first results to show that treating CORT rats with the TNF-alpha antagonist Enbrel can produce reversals in both object-location and object-in-place memory, ostensibly through restoring function in the hippocampus and pre-frontal cortex.

48. Organizational influences of sex steroid hormones on corticosteroid and glucocorticoid receptor responses in male and female Long Evan rats. Leyla Innala BSc1, Yi Yang BSc1, Adam Anonuevo MS1, and Victor Viau PhD1. 1Department of Cellular and Physiological Sciences, University of British Columbia, BC, Canada. Previous findings in our lab indicate that altering the sex

steroid milieu during the neonatal period in the rat can permanently change or organize the capacity of adult animals to show repeated stress-induced declines in hypothalamic-pituitary-adrenal (HPA) axis responses (Bingham et al., 2011, Psychoneuroendocrinology). We are currently examining how androgen receptor blockade in males and testosterone treatment in females during the postnatal period can organize corticosteroid responses to acute and repeated restraint exposure. Our preliminary studies show that the decline in HPA axis responses to repeated restraint is paralleled by decrements in glucocorticoid receptor activation in the hippocampus. Thus, we are also following the extent to which neonatal androgens interact on GR responses in adulthood. As we intend on extending this analyses to other putative glucocorticoid negative feedback regulators of the HPA axis, we hope to reveal the sex- and region-specific nature by which the sex steroid hormones may come to permanently alter adaptive neuroendocrine responses. Research supported by the National Sciences and Engineering Council of Canada (NSERC) and Canadian Institutes of Heath Research (CIHR) grants to VV.

49. **Anxiety vulnerable individuals exhibit enhanced classical eyeblink conditioning when trial timing is uncertain: support for a learning diathesis model of anxiety disorders.** M.T. Allen1,2, C.E. Myers2,3, & R.J. Servatius2,3 1University of Northern Colorado 2Rutgers University 3 Dept. of Veterans Affairs, NJ Healthcare System Personality factors such as behavioral inhibition have been found to enhance associative learning in classical eyeblink conditioning and may be a diathesis for anxiety disorders. We recently reported that enhanced acquisition of conditioned eyeblinks in individuals self-reporting behavioral inhibition was more evident in an omission / yoked protocol in which the US was omitted on a CR trials (Holloway et al., 2014) and in partial reinforcement protocols with 50% paired trials (Allen et al., 2014) than in standard 100% CS-US paired training. In both omission / yoked protocols and partial reinforcement protocols, there is some degree of uncertainty as to when the next air puff will occur. The exclusion of the air puff on some trials also extends the inter-trial interval (i.e., ITI) between tone-air puff training trials. Therefore, uncertainty and/or trial spacing effects may underlie our previous findings of enhanced associative learning in behaviorally inhibited individuals. In the current study, we tested the hypothesis that spacing trials by extending the ITI from 30 s to 57 s would facilitate learning. We also tested the hypothesis that uncertainty about trial timing would facilitate learning in behaviorally inhibited individuals by utilizing a long variable ITI that ranged between 25 and 123 s (mean 57 s). Eighty nine participants completed personality inventories (i.e., the Adult Measure of Behavioral Inhibition). Participants were grouped as behaviorally inhibited (i.e., anxiety vulnerable) and non-inhibited based on a median split of the AMBI scores. Delay eyeblink training consisted of 30 paired CS-US trials (500 ms/1200 Hz pure tone CS overlapping and co-terminating with a 50 ms, 5 psi corneal air puff US). Eyeblink responses were measured via silver chloride EMG electrodes. Anxiety vulnerable individuals exhibited facilitated acquisition as compared to non-vulnerable individuals. High AMBI individuals exhibited facilitated learning to the spaced trials with a variable inter-trial interval ranging from 25 to 123 s, but not with the 30 s or fixed 57 s ITI. This finding is consistent with previous findings from omission/yoked and partial reinforcement protocols in which the time between CS-US paired trials varied across the training session. Overall, enhanced sensitivity to forming stimulus associations in anxiety vulnerable individuals is most evident when the predictive relationship between the CS and US is uncertain.

50. **Disinhibition of prefrontal cortex differentially gates hippocampal and amygdala inputs to the nucleus accumbens.** Maric T. Tse1, Stan B. Floresco1**.** 1Department of Psychology and Graduate Program in Neuroscience, University of British Columbia**.** Pathophysiological alterations in prefrontal cortex (PFC) GABA transmission have been proposed to underlie various psychiatric disorders. Previous studies in our laboratory have revealed that pharmacological reduction of PFC GABA activity can produce a variety of cognitive, affective and dopaminergic abnormalities that resembles schizophrenia, including impaired spatial memory (mediated by the hippocampus) and aberrant attributions of salience to fear-related stimuli (mediated by the amygdala). Inputs from the PFC, hippocampus and amygdala converge within the nucleus accumbens (NAc), yet the manner in which disinhibitory increases in PFC outflow may affect integration of cognitive and emotional information arising from these temporal lobe inputs remains to be elucidated. In the present study, we recorded from NAc neurons that that received inputs from either the hippocampus or the basolateral amygdala (BLA) in urethane-anesthetized rats. Under basal conditions, stimulation of fimbria/fornix (conveying

hippocampal output) and the BLA reliably evoked spike firing in separate populations of NAc neurons. Disinhibition of the PFC via local infusion of the GABA-A antagonist bicuculline (25-50ng) reliably attenuated hippocampal evoked firing. In contrast, reducing PFC GABA transmission did not reduce firing evoked by BLA stimulation in a separate population of cells, and actually lead to an enhancement in evoked firing in some neurons. This suggests that reduced PFC GABA activity may differentially gate mnemonic versus emotional signals originating from the temporal lobes and converging in the NAc. Furthermore, they suggest perturbations in PFC GABA transmission that may occur in schizophrenia may lead to altered gating of these inputs to the NAc. This in turn may contribute to impairments in hippocampal-mediated cognitive function and aberrant affective salience attribution and increased anxiety observed in the disorder.

51. **Adolescent social defeat alters tyrosine hydroxylase activity in distinct cortical and subcortical regions of the young adult brain.** Matthew A. Weber1, Jamie L. Scholl1, Riley T. Paulson1, Gina L. Forster1, Kenneth J. Renner2, and Michael J. Watt1**.** 1Center for Brain and Behavior Research (CBBRe), Division of Basic Biomedical Sciences, Sanford School of Medicine and 2Biology Department, University of South Dakota, Vermillion, SD USA**.** Adolescent social defeat in rats, a model for early-life aversive experiences, results in decreased medial prefrontal cortex (mPFC) dopamine (DA) activity in early adulthood. The precise mechanisms influencing this decrease in mPFC DA activity after adolescent defeat are not fully understood, but may involve changes to activity of tyrosine hydroxylase (TH), the rate-limiting enzyme in DA synthesis. Here, we used two experimental approaches to examine TH activity in specific regions of the young adult brain following adolescent defeat. In the first, brain tissue collected from previously defeated and control rats in early adulthood (postnatal day [P]56) was processed using western immunoblot for both total TH expression and levels of phosphorylated serine 40 TH (pSer40 TH). In the second, previously defeated and control rats received acute injections of the amino acid decarboxylase (AADC) inhibitor NSD-1015 (100 mg/kg, ip.) at P56, with brain tissue accumulation of the DA precursor DOPA as measured by HPLC-EC serving as a measure of in vivo TH activity. Activity of TH in the adult mPFC was increased following adolescent defeat, as indicated by higher expression of pSer40 TH relative to total TH. This increase in mPFC TH activity was also shown by greater DOPA accumulation 30 min after AADC inhibition. Within subcortical regions, AADC inhibition elicited greater DOPA accumulation 180 min after injection in the striatum of previously defeated rats, indicating higher in vivo TH activity, with a similar effect seen in the nucleus accumbens (NAc) core at 30 min. No differences in DOPA accumulation as a result of adolescent defeat were evident in the NAc shell or the dopaminergic cell body regions. The increase in adult mPFC TH activity following adolescent defeat is contrary to our initial hypothesis that TH activity would be decreased to result in lower mPFC DA activity. We speculate that the increased mPFC TH activity may be acting as a compensatory mechanism in an attempt to raise DA synthesis in the mPFC and restore homeostasis. Our results also suggest adolescent defeat has effects on DA terminal fields beyond the mPFC, but the functional significance of these changes to subcortical TH activity remains to be elucidated. Funding Support: NSF IOS 1257679 (MJW), NIH NIDA R15 DA035478 (MJW), NIH NIDA RO1 DA019921 (GLF), and NSF IOS 0921874 (KJR)

52. **Prefrontal GABA-A and NMDA receptor modulation of working memory assessed with a delayed non-match to position task.** Meagan L. Auger1 & Stan B. Floresco1**.** Department of Psychology, University of British Columbia**.** Abnormalities in prefrontal GABA and NMDA receptor function are thought to contribute to cognitive symptoms associated with schizophrenia. Recent work from our group has shown that prefrontal GABA-A receptor antagonism produces a number of cognitive abnormalities relevant to the disorder in rats. However, this manipulation did not produce impairments when working memory was assessed with a delayed-response version of the radial arm maze task. Notably, performance of this task is self-paced, while delayed-response tasks used in patients often present multiple trials in quick succession and with short delays, placing higher demands on attention. As such, this study aimed to assess the contribution of prefrontal GABA and NMDA receptor signaling to this type of working memory task. Male Long Evans rats were trained in an operant delayed non-match to position task. The task consists of a sample phase, in which one of two levers is extended, and a choice phase that require selection of the opposite lever, separated by a variable delay (1-24 s). Well-trained rats received counter-balanced intra-medial PFC infusions of

saline or drug. Inactivation of the PFC using GABA agonists baclofen and muscimol (100 ng each) produced delay-independent impairments on the task. Intra-mPFC infusion of the GABA-A antagonist bicuculline produced dose-dependent effect, with the higher dose (50 ng) causing delay-independent impairments. Antagonism of prefrontal NMDA receptors using MK-801 also disrupted working memory in a dose dependent manner, with a higher dose (6 ug) producing delay-dependent impairments. In comparison, NR2B-specific NMDA receptor antagonism using Ro-25-6981 (2.5 ug) did not impair performance of the task. Taken together, these findings indicate the optimal prefrontal GABA-A and NMDA receptor function are necessary for working memory processes. Furthermore, they suggest that pertubations in both GABA and glutamate signaling within the frontal lobes may contribute to impairments in short-term working memory functions that are observed in schizophrenia.

53. **"Gut feelings": Vagal afferent signaling modulates behavioral flexibility in rats.** Melanie Klarer1, Myrtha Arnold1, Jean-Philippe Krieger1, Wolfgang Langhans1 and Urs Meyer1,2**.** 1Physiology and Behavior Laboratory, ETH Zurich, Switzerland. 2Veterinary Pharmacology and Toxicology, University Zurich, Switzerland. The central nervous system and viscera are engaged in constant bidirectional communication via diverse neural, immune, and endocrine pathways. This functional entity allows "top-down" and "bottom-up" information flow pertaining to the regulation of body homeostasis and control of ingestive behavior. It has long been speculated that afferent signals from the viscera may also modulate other behaviors that go beyond food intake. Our group has recently provided direct evidence for this hypothesis by demonstrating alterations in innate anxiety and learned fear following subdiaphragmatic vagal deafferentation (SDA) in rats. SDA is the most complete and selective disconnection of abdominal vagal afferents as it eliminates all abdominal vagal afferents while sparing half of the vagal efferents. In the present study, we aimed to explore the effects of SDA on behavioral flexibility. Two different behavioral paradigms were used for this propose, namely (1) reversal of positively reinforced left-right discrimination and (2) latent inhibition (LI) in the conditioned taste aversion (CTA) test. The ability to recognize an unexpected consequence from a previously established associative learning rule, and then to switch the response contingency accordingly, is crucial to both discrimination reversal learning and LI. We found that Sham and SDA rats did not differ in the acquisition of positively reinforced left-right discrimination learning. Compared to Sham controls, however, SDA rats exhibited faster reversal learning following completion of the acquisition criterion. Consistent with these effects, SDA did not affect conditioning per se in the CTA test, but it abolished LI via selective effects in CS-pre-exposed animals. Additional neurochemical investigations showed that SDA rats displayed increased basal levels of dopamine in the ventral striatum, a key brain area involved in certain forms of behavioral flexibility. Together, our results suggest that SDA facilitates behavioral and/or cognitive switching between different response contingencies without affecting basic discrimination learning or classical conditioning. These effects may involve altered dopaminergic signaling in the ventral striatum.

54. **Inactivation of the orbitofrontal cortex reduces irrational choice on a rodent Betting Task.** Michael M. Barrus1, Jay G. Hosking2, Paul J. Cocker1, Catherine A. Winstanley1. 1University of British Columbia, 2Harvard University. The neurobiology of cognitive biases is not well understood, though they may play a significant role in disorders of decision making such as pathological gambling. Understanding the neurobiology of these biases could lead to more effective pharmacological and therapeutic treatments for disorders in which aberrant decision making is prominent. The rat Betting Task (rBT) was designed to examine risk aversion in rodents; in the task, the animal is presented with a choice between two options with equivalent expected value, where one option is guaranteed while the other has a 50% chance of double or nothing. Past work has shown that a subset of animals (termed wager sensitive) adopt an irrationally risk averse choice preference in which they shift their choice away from the uncertain option as the bet size grows larger. It has been demonstrated that this pattern of risk aversion is related to lower D2/3 receptor binding in the striatum, but it is likely that additional regions are involved with this bias. Here, the orbitofrontal cortex (OFC), the prelimbic cortex (PL), and the infralimbic cortex (IL) were inactivated to examine their putative role in the rBT. Inactivation of the OFC (but not the IL or the PL) ameliorated the pattern of irrational risk aversion characteristic of wager-sensitive animals, but did not affect choice in the non-wager sensitive animals. This finding suggests that the OFC may play a role in cognitive biases, especially those related to subjective value.

55. Cortical circuitry underlying emotional memory to predatory threats. De Lima, M.A.X.; Canteras, N. S. Department of Anatomy, Institute of Biomedical Sciences, University of São Paulo**.** The dorsal premammillary nucleus is particularly responsive to predatory threats and is known to influence contextual memory through its projections to the ventral part of the anteromedial thalamic nucleus (AMv). Recent studies from our laboratory indicates that the AMv influences the acquisition, but not the expression, of contextual conditioned defensive reactions to predatory threats. The AMv is known to provide strong projections to the hippocampal formation (influencing both the medial and lateral perforant pathways) and to a number of cortical fields, including the anterior cingulate (ACA), prelimbic (PL), retrosplenial (RSP) and posteromedial visual area (VISpm). In the first part of the present study, using the anterograde biotinylated dextran amine (BDA), we investigated the connections of these cortical areas targeted by the AMv. Interestingly, we have found that these areas are particularly interconnected and provide important inputs to the hippocampal formation, forming a cortical network that should process predatory threats and transmit this information to the hippocampus. To test whether this cortical network would influence the processing of contextual memory to predatory threats, in the second part of this study, we placed in each one of these cortical fields bilateral cytotoxic lesions by injecting N-Methyl-D-aspartate (NMDA). We found that neurochemical lesions placed in the ACA, PL, RSP or VISpm areas altered the learned defensive responses to predatory context, but did not influence the innate defensive behavior during direct exposure to the predator. Overall, the present investigation helps to reveal a cortical network seemingly influenced by predatory threats that is involved in the processing of contextual fear conditioning to predatory threats.

56. **Interactions of behavioral training and ketamine administration on changes in parvalbumin positive neurons.** Monica M. Bolton1, Chelcie F. Heaney1, Andrew S. Murtishaw1, and Jefferson W. Kinney1. 1University of Nevada, Las Vegas. Ketamine is a high affinity non-competitive antagonist of the ionotropic N-methyl-D-aspartate (NMDA) glutamate receptor. Several previous investigations in our laboratory using chronic (15 days) subanesthetic administration of ketamine have demonstrated learning and memory deficits in rodents. We have also repeatedly observed an increase in the number and altered position of parvalbumin (PV) positive neurons in the CA3 field of the hippocampus in ketamine treated animals. In addition, numerous recent clinical studies have demonstrated a rapid-acting antidepressant effect of subanesthetic ketamine. We were interested in examining if an increase in PV neurons may be contributing to ketamine's antidepressant effect. To understand the mechanism through which ketamine activation results in an increase in PV neurons, we performed an experiment to inhibit the mTOR signaling pathway using rapamycin. The same chronic, subanaesthetic dose and administration of ketamine was performed for 15 days along with bilateral hippocampal infusion of rapamycin (inhibitor of mTOR signaling pathway). Forced swim test was performed to examine the antidepressant effects of ketamine. Animals increased their struggle time after chronic administration of ketamine while ketamine/rapamycin did not significantly increase their struggle time compared to saline. Interestingly, ketamine administration and forced swim testing did not produce the same increase in PV number and position observed in previous learning and memory investigations. This study indicates that in addition to ketamine administration, a task involving either behavioral engagement or a motoric component may be necessary to observe a change in PV neurons.

57. Assessing the treatment predictive validity of model animals of bipolar mania. Morgane Milienne-Petiota,b, Jordy van Enkhuizena,b, Mark A. Geyera,c, and Jared W. Younga,c*. a Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804. b Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands. c Research Service, VA San Diego Healthcare System, San Diego, CA. Introduction: Bipolar Disorder (BD) is a disabling and life-threatening illness occurring in approximately 1-2% of the population, characterized by fluctuations of mood states from mania to depression. Current treatments for BD have limited efficacy in part due to the fact that all were found serendipitously resulting from limited mechanism-relevant model organisms of BD. BD patients have polymorphisms of the dopamine transporter (DAT), reducing levels in unmedicated patients. Reducing functional DAT levels by pharmacological or genetic means

results in a behavioral profile that closely resembles BD mania with some predictive validity. To date however, neither risperidone (Risp) nor lithium (Li) have been assessed. We therefore examined the efficacy of chronic Li or Risp to remediate the mania-relevant behavior of these model animals. Methods: DAT knockdown (KD) and their wildtype (WT) littermates (2 cohorts) were treated with the antipsychotic Risp (0.03 or 0.3 mg/kg/day; 28 days), or Li (600 mg/L; 10 days). C57BL/6J mice (C57; 2 cohorts) were treated with acute GBR12909 (GBR; 9 or 13 mg/kg) preceded by Risp (0.3 mg/kg/day; 28 days) or Li treatment (1 g/L; 7 days). All animals were then tested in the Behavioral Pattern Monitor (BPM) for 60 min. Results: DAT KD and GBR-treated C57 mice exhibited a behavioral profile consistent with BD mania and as previously reported: Increased transitions, increased specific exploration, and reduced spatial d. Risp did not affect the activity of DAT KD or WT mice as measured by transitions [Risp; $F(2,38)=0.2$, $p=0.8469$; Risp X gene $F<1$, ns], or specific exploration [$F<1$, ns]. Similarly, no Risp effect was observed on spatial d and no interaction [$F<1.2$, ns]. Similarly, no effects were observed when Risp was administered to GBR-treated C57 mice [$F<1$, ns]. In the Li study, the DAT KD mania-relevant profile remained intact irrespective of 600 mg/L Li treatment. In the C57 GBR study however, with 1g/L Li, post hoc analyses revealed that Li X GBR treated mice no longer exhibited increased transitions or holepoking ($p>0.1$), although lower spatial d was still observed ($p<0.05$) compared to vehicle. Conclusions: Reduced DAT functioning recreated the mania-like exploratory profile in mice. Neither risperidone (28 mg/kg/day) nor lithium (600 mg/L) normalized the mania-like behavior displayed by DAT KD mouse model of BD mania. Risperidone (28 mg/kg/day) also did not attenuate the mania-like behavior of mice treated with GBR12909. In contrast however, a higher dose of lithium (1 g/L) attenuated the effects of GBR12909 on exploration and activity. Serum concentration studies support the need for 1 g/L of lithium to reach concentrations required for the treatment of mania. The DAT KD lithium study will be repeated at this higher dose, while the data presented here partially supports reduced functioning of the DAT as a model organism predictive of treatment effects in mania.

58. **Does sleep play a role in event cued prospective memory? Exploring the role of cue encodings.** Singh, T & Kashyap, N**.** Indian Institute of Technology Guwahati, India**.** The dynamic nature of the world requires adaptation which depends on acquiring, strengthening and higher level organization of new memories. Recent work suggests that sleep modulates different forms of memory reorganization (Rash & Born, 2013; Stickgold & Walker, 2013; Diekelman & Born, 2010). Event cued prospective memory is dependent on successful cue–action retrieval in future. Cues are central to event based prospective memory & encoding of cues hold the key to successful retrievals of cue-action pair. Research on memory suggests explicit and implicit encodings of cues differentially effect recognition memory for these cue. Recent findings also reveal facilitatory role of sleep on event cued prospective memory**.** Objective: The objective of the present study is to – a) Evaluate the effect of one night of undisturbed sleep on event cued prospective memory; b) Evaluate the role of explicit & implicit encodings of cue on event cued prospective memory; & c) Establish the role of sleep on cue encodings in event based prospective memory. Data: Ten healthy paid participant (mean age: 22.5 yrs, all males) participated in the study. Each participant spent one adaptation & two experimental nights (undisturbed & deprived sleep) in the sleep laboratory, separated by at least one fortnight. On each experiment night participants completed learning phase of behavioural task followed by sleep or wakefulness & subsequent retrieval forty eight hours later. Results: Accuracy data (retrieval) was entered into 2 group (sleep, wake) x 2 encoding (explicit, implicit) repeated measure ANOVA. Significant main effects of condition [$F(1, 9) = 14.28$, $p = 0.007$, $\mu2 = 0.67$], encoding [$F(1, 9) = 20.51$, $p = 0.003$, $\mu2 = 0.74$] and group x encoding interaction ($p = 0.01$) was reported. Interaction were followed up by computing simple mean effects (LSD) which revealed stronger encoding differences in the sleep group ($p < 0.001$) than the wake group ($p = 0.06$). Conclusion: The above results conclude that one night of sleep as compared to sleep deprivation benefits event cued prospective memory. Further cue encodings played a significant role in sleep dependent prospective memory retrieval with implicit cues showing better encodings than explicit cues.

59. **D1 /D2 receptor modulation of risk/reward decision-making in prefrontal-subcortical circuits.** N.L. Jenni1, J.D. Larkin1, & S.B. Floresco1. 1Department of Psychology, University of British Coloumbia. We routinely face decisions that require weighing the relative costs and benefits associated with different rewards in order to select better courses of action. Nodes within the

mesocorticolimbic dopamine system interact in situations of reward uncertainty to guide risk/reward decisions. Work from our group has shown that D1/D2 receptor modulation within the prefrontal cortex (PFC) increases or reduces preference for large/risky options in opposing ways. Recent work suggests that there are different populations of prefrontal neurons that exclusively express either D1 or D2 receptors. Here, we investigated whether these distinct prefrontal D1 or D2 expressing neurons may differentially modulate risk/reward decisions, via distinct subcortical output pathways. Decision-making was assessed using a probabilistic discounting task. Rats were well-trained to choose between levers that delivered small/certain or large/uncertain rewards—the odds of which decreased systematically across 4 blocks of discrete-choice trials (100% -12.5%). We used asymmetrical unilateral infusions of a D1 or D2 antagonist into one hemisphere of the PFC, in combination with a contralateral inactivation of the nucleus accumbens (NAc) or basolateral amygdala (BLA) to selectively disrupt D1 or D2 communication between the PFC and these output regions. Selectively disrupting D1 modulation of PFC-NAc circuits (but not PFC-BLA projections) reduced preference for the large/risky option. This was due to a reduction in reward sensitivity, meaning they were less likely to follow receipt of a risky win with another risky choice. In contrast, preliminary results indicated that disrupting PFC D2 communication with the BLA increased preference for the large/risky option. This was primarily due to a reduction in negative feedback sensitivity, meaning the rats were more likely to follow a non-rewarded risky choice with another risky choice. These findings suggest that PFC dopamine may modulate different aspects of risk/reward decision-making via actions on separate prefrontal D1 and D2 receptor-mediated pathways to distinct subcortical regions. Abnormal decision-making is prominent in disorders characterized by perturbations of the dopamine system. Understanding the neurological underpinnings of these behaviours may provide insight into the pathophysiology underlying these disorders.

60. **The effect of minocycline pre-treatment on nicotine-induced alterations during periadolesence of neuronal ΔFosB expression in limbic areas of the rat brain.** Partha S. Nagchowdhuri, Kristen T. Lane, Helen L. Williams, and Brian A. McMillen**.** Department of Pharmacology and Toxicology, Brody School of Medicine at East Carolina University, Greenville, North Carolina 27834 USA**.** Nicotine use during adolescence is considered to be a 'gateway' that leads to the brain's sensitization to other illicit substances in the future. Psychoactive drugs such as nicotine are known to induce the expression of the transcription factor ΔFosB that facilitates this sensitization process. A previous study from our laboratory showed that a once daily, 10-day administration of nicotine that bracketed the onset of puberty in rats (PND 35-44) at an intraperitoneal (i.p.) dose of 0.4 mg/kg induced the expression of ΔFosB in selected memory and reward subset areas of the rat brain. Further, this expression persisted into adulthood (PND 80), especially in the nucleus accumbens (NAc) and dentate gyrus of hippocampus (DG) (Soderstrom et al. 2007). Our long-term goal is to extend the previous study by elucidating the role of microglia in this sensitization process in vivo. Further research is needed to determine whether there is a linkage between microglia activation and ΔFosB induction. In this study, minocycline, a lipophilic tetracycline antibiotic commonly used to suppress the activation of microglia, was injected into periadolescent male Sprague-Dawley rats prior to nicotine administration to assess the impact of microglial activation on ΔFosB induction by nicotine. Similar to the report by Soderstrom and colleagues, 0.4 mg/kg i.p. of nicotine-bitartrate (all doses are as free base) for the 10 days that bracket the onset of puberty (PND 35-44) increased the density of ΔFosB immuno-labeled neuronal nuclei in the DG from the control by 34% ($n=4$, $p<0.05$; one-way ANOVA and Dunnett's t-test). Minocycline-HCl pre-treatment 30 minutes prior to each dose of nicotine at a dose of 30 mg/kg i.p. reduced the density of ΔFosB labeled nuclei by 15% from nicotine treatment alone and the change was not different from control ($n=4$, $p>0.05$, Dunnett's t-test). Thus, minocycline pre-treatment reduced the ability of nicotine to increase the expression of ΔFosB in the DG. This study will further analyze the effect of minocycline on ΔFosB induction in the NAc, prefrontal cortex (PFC), and the ventral tegmental area (VTA).

61. **Impact of CRHR1 blockade on BDNF and TrkB immunohistochemical expression in the hippocampus, amygdala and hypothalamus: relationship to spatial memory and fear learning following global cerebral ischemia in rats.** Patricia B. de la Tremblaye1, Simon Benoit1, Hélène Plamondon Ph. D1. 1Behavioural Neuroscience Group, School of Psychology, University of Ottawa. Elevated and prolonged stress leads to increased brain derived neurotrophic factor (BDNF) and its

receptor TrkB in some regions of the brain, e.g. the BLA, but decreases in other regions such as the CA1 subfield of the hippocampus and dendritic spine density increases or decreases in line with these changes in BDNF, a process thought to be mediated by corticotropin-releasing hormone type 1 receptor (CRHR1) activation. The current study evaluated the role of CRHR1in ischemia-induced behavioral impairment and key neuroplasticity markers. Forty-eight male Wistar rats (n=12 per group) were subjected to sham surgery or global cerebral ischemia using the four vessel occlusion (4VO) model. ICV injection of Antalarmin (2µg/2µl) or saline was administered 30 min prior to ischemia. Rats were then assessed for fear and spatial learning in a Y-Maze inhibitory avoidance task, and in the Barnes Maze, respectively. Thirty days post reperfusion, a histological analysis of viable cells was completed in the CA1 and BLA. The expression of BDNF and TrkB was detected by fluorescence immunostaining in the hippocampus, basal lateral amygdala (BLA) and the paraventricular nucleus of the hypothalamus (PVN). Ischemic-Antalarmin rats showed improved spatial memory in the Barnes Maze test (latency, distance traveled) and enhanced fear memory in the Y-Maze. Antalarmin was also neuroprotective for in the CA1but not the BLA and global ischemia led to increased BDNF and TrkB mRNA and protein levels in the amygdala, but decreased in other regions such as the hippocampus. Contrary to what is observed in stress paradigms, hippocampal BDNF and TrkB expression remained significantly elevated 30 days post ischemia. Antalarmin treatment reduced such elevation to comparable levels to that observed in the sham and control groups. At the PVN but not in the BLA, we observed a lasting heightened BDNF and TrKB expression, which appeared regulated via post-ischemic CRHR1 signaling. These findings suggest that CRHR1 activation contributes to CA1 neuronal injury and changes in BDNF and TrkB expression in discrete brain region of the stress system post ischemia, and that blockade of these receptors prior to ischemia is beneficial for post-ischemic neuronal and cognitive recovery.

62. **Depressive-like behavior in mice lacking the low-density lipoprotein receptor.** Patricia Souza Brocardo1,2, Daiane Engel1,3, Ana Lúcia Severo Rodrigues1,3 and Andreza Fabro de Bem 1,3**.** 1Centro de Ciências Biológicas, 2Departamento de Ciências Morfológicas, Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, Brazil, 3Departamento de Bioquímica, Universidade Federal de Santa Catarina, Florianópolis, Santa Catarina, Brazil. Introduction: Familial hypercholesterolemia is the most common cause of inherited high cholesterol, which results from mutations in the low-density lipoprotein (LDL) gene. Several studies have been showing the association between increased serum cholesterol and signs of depressive mood. Objectives: To investigate the association of hypercholesterolemia and depressive-like behavior in mice lacking the low-density lipoprotein receptor. Materials and Methods: Three-month-old male and female C57BL/6 and LDLr–/– mice were divided in four experimental groups and treated with fluoxetine (7 days via oral (p.o) by gavage 10 mg/kg) or vehicle: Group 1- C57BL/6 wild-type vehicle group; Group 2- C57BL/6 wild-type fluoxetine; Group 3- LDLr−/− vehicle group; and Group 4- LDLr−/− fluoxetine group. Seven days after treatments, the animals were tested in behavioral tests (except by the sucrose intake test which was carried out during treatments). Independent groups of animals were used in each tests; n = 7 to 10 animals per experimental group. After the performance on behavioral tasks, 6-9 animals in each group had its cortex and hippocampus dissected to determine the MAO activity. Results: LDLr-/- mice show anhedonic behavior evaluated by the decrease in sucrose consumption as compared to wild-type group. However, the treatment of mice with fluoxetine (10 mg/kg, p.o.), was not able to restore the sucrose intake in LDLr-/- animals, showing that the anhedonic phenotype of this group is not sensible to antidepressant treatment. In addition, we evaluated self-care and motivational behavior using the splash test. LDLr-/- mice display increased latency time to the first grooming when compared with the wild-type mice. Importantly, fluoxetine treatment reversed the increased latency to grooming. During the tail suspension test (TST) the LDLr-/- mice presented increased immobility time and repeated fluoxetine antidepressant treatment significantly reversed this behavior. Conclusions: The present study suggests that higher cholesterol concentrations are associated with signs of depressive mood. Funding acknowledgements: CNPq and FAPESC, Brazil.

63. **Chronic administration of the D2-like agonist ropinirole galvanises behaviour on a rodent slot machine task: Toward a rodent model of problem gambling.** Cocker, PJ1, Tremblay, MT1. & Winstanley, CA1. 1 Department of Psychology, University of British Columbia, 2136 West Mall,

Vancouver, BC V6T 1Z4, Canada**.** Gambling is an enjoyable and harmless past-time for many, but for some it can become a maladaptive compulsion akin to drug or alcohol addiction. Despite increasing recognition that the phenomenological process underlying both substance and behavioural addictions may be similar, legislation surrounding gambling is being progressively relaxed and consequently access to gambling opportunities continue to rise. This is particularly concerning, not just as data suggests that levels of disordered gambling (DG) are well correlated with accessibility of gambling opportunities, but also as there are currently no dedicated treatment options for DG. Animal models offer an opportunity to not only study the underlying neurobiology of disorders such as gambling, but may also offer insights into treatment options. To that end we have developed a rodent slot machine that suggests rats share key behavioural features with human gamblers. Data from the rodent slot machine task (rSMT) suggests that the dopamine D2-like receptor family is critically involved in modulating task performance. Such findings are congruent with an established role for dopamine in mediating reward associated learning. Moreover, increasing clinical reports suggest that administration of D2-like agonists such as ropinirole to patients with Parkinson's disease is associated with compulsive behavioural problems including DG. A rodent model of DG would represent an invaluable assay, not only to screen novel treatments for DG, but also potentially inform more directed pharmacotherapies for Parkinson's disease. Here, we suggest that chronic administration of a D2-like agonist may represent a novel analogue of problematic gambling in rodents. Osmotic mini-pumps delivering the D2-like agonist ropinirole or saline were implanted into a group of animals trained on the rSMT. Administration of ropinirole did not impair the animals' responsiveness to putative winning signals on the rSMT. However, it did produce a robust increase in the number of trials animals completed per session, suggesting ropinirole administration galvanised game play. Although preliminary, such data could be considered analogous to the compulsive style of play exhibited by problem gamblers.

64. **Organic cation transporter 3 is expressed on neurons and glia in the amygdala: A mechanism for stress-induced modulation of amygdala activity.** Jonathan E. Hill1, Joan Chan2, Matthew Hurley1, Virginia M. Pickel2, Paul J. Gasser1**.** 1 Department of Biomedical Sciences, Marquette University. 2 Brain & Mind Research Institute, Weill Cornell Medical College. Dopamine exerts powerful modulatory influences over fear and anxiety behaviors by controlling the activity and excitability of neurons in the BLA. Acting primarily through D1 receptors, dopamine increases the activity of BLA pyramidal neurons by attenuating inhibitory influence from the infralimbic prefrontal cortex (PFC) and enhancing sensory cortical inputs, resulting in overall enhancement of BLA-mediated behaviors. Dopaminergic neurotransmission in the amygdala occurs through a combination of synaptic, peri-synaptic, and long-distance volume transmission. Thus, mechanisms, including transport mechanisms, that regulate extracellular dopamine concentrations in the amygdala, are likely to be important determinants of amygdala function. We have demonstrated the expression of organic cation transporter 3 (OCT3), a high-capacity transporter for dopamine and other monoamines, throughout the rat brain. OCT3-mediated transport is inhibited, directly and acutely, by corticosterone. In this study, we used immunochemical techniques at both the light and electron microscopic level to examine a) the distribution and phenotype of OCT3-expressing cells; b) the subcellular localization of OCT3; and c) the spatial relationships of OCT3 to dopaminergic markers in the rodent amygdala. We observed high densities of OCT3-immunoreactive perikarya and punctae throughout the D1 receptor-rich main, anterior and paracapsular ITCs; and lower densities in the basolateral and central nuclei. OCT3-ir in ITCs was observed proximal to D1 receptor immunoreactivity. Tyrosine hydroxylase-immunoreactive fibers in the ITC were immunonegative for OCT3, though OCT3-immunoreactive punctae were observed in close proximity to TH+ terminals. OCT3-immunoreactive neurons and glia were observed in all amygdala subregions. In the BLA, OCT3-immunoreactive cells also expressed parvalbumin, calretinin, or calbindin. At the EM level, OCT3 immunostaining was associated with glial processes, and with plasma membranes of dendritic spines adjacent to putative monoamine release sites. In several dendrites, dense OCT3 immunostaining was associated with mitochondria adjacent to the plasma membrane. Dense OCT3-immunostaining was also associated with the nuclear envelope. These data suggest that OCT3 represents a post- or peri-synaptic clearance mechanism, and raise interesting questions regarding potential roles of this transporter in the intracellular disposition and metabolism of substrates. Inhibition of OCT3-mediated transport by corticosterone

may represent a mechanism by which acute stress alters dopaminergic neurotransmission in the amygdala, leading to alterations in fear and anxiety-like behavior.

65. **Immunization with the immunoregulatory saprophytic bacterium, Mycobacterium vaccae, enhances fear extinction in adult male Sprague Dawley rats.** Philip H Siebler1, James H Fox1, James E Hassell1, Christopher A Lowry1. 1University of Colorado Boulder Department of Integrative Physiology & Center for Neuroscience. Several stress-related psychiatric disorders, such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD), are characterized by increased inflammation, which is thought to increase vulnerability to these conditions and to contribute to psychiatric symptoms. One potential therapeutic approach to treatment of stress-related psychiatric disorders is the use of bioimmunoregulatory approaches that can induce a sustained suppression of inflammation. Immunization with antigens derived from a heat-killed preparation of the pseudocommensal saprophytic bacterium, Mycobacterium vaccae, has been shown to induce proliferation of regulatory T cells (Treg) and production of anti-inflammatory cytokines. In order to determine if M. vaccae immunization can influence subsequent fear expression or fear extinction, we conducted studies using the fear-potentiated startle paradigm in adult male Sprague Dawley rats. Rats arrived in the vivarium 42 days before the start of behavioral testing and were pair housed throughout the study. On Day –38, rats were tested for baseline acoustic startle then matched and assigned to treatment groups. Rats were immunized with M. vaccae (0.1 mg in 100 µl, s.c.), or vehicle (borate-buffered saline), on Days –35, –28, and –21 days prior to behavioral testing. All rats were tested for baseline acoustic startle responses on days 1 and 2, then exposed to fear conditioning on days 3 and 4. For fear conditioning, rats were allowed a 5 min acclimation period followed by the presentation of the first of 10 conditioned (CS, light; 115 lux) - unconditioned stimuli (UCS, foot shock) pairings (variable ITI = 4 min; 3-5 min range). The light lasted for 3.7 seconds and co-terminated with the foot-shock (0.6 mA, 0.5 seconds). Rats were tested for fear-potentiated startle on Day 5, and extinction on Days 6-10. Immunization with M. vaccae had no effect on baseline startle, measured on Days 1 or 2, or fear acquisition, measured on Day 5. However, rats immunized with M. vaccae responded with enhanced fear extinction, both across days and within session. These data support further studies of bioimmunomodulatory approaches to the prevention and treatment of stress-related psychiatric disorders. Acknowledgements: The project described was supported by award number NSF-IOS #0845550.

66. **Age-related changes in frailty in two mouse models of Alzheimer's disease.** Brown, Richard E. and Shin Sooyoun. Departments of Psychology and Neuroscience, Dalhousie University, Halifax, Nova Scotia, Canada. Frailty is a measure of the accumulation of age-related physical deficits [Howlett SE, Rockwood K. 2013. Age Ageing. 42, 416-423]. Although the concept of frailty was developed for humans, the Frailty Index (FI) can also be used to assess age-related disabilities in mice. The mouse FI consists of 31 health-related variables (integument, digestive, ocular, auditory, urogenital, respiratory systems, signs of sickness, abnormalities in body temperature and weight) [Whitehead J et al., 2014. J Gerontol A. 69, 621-632], with higher FI scores indicating increased frailty. We found significant differences in the lifespan of 3xTgAD and 5xFAD mouse models of AD compared to their wildtype controls. In order to have a measure of aging that was independent of chronological age, we calculated the FI for all of the mice from 3-28 months of age in our animal colonies. FI score was positively correlated with age in both the 5xFAD and 3xTgAD mice and, in both genotypes, males had higher FI scores than females. The 5xFAD mice had higher FI scores than their wildtype (C57BL6xSJL) controls, but there was no difference in their rate of deficit accumulation. The 3xTgAD mice had a higher rate of deficit accumulation than their wildtype (B6129S/F2) controls, indicating that they have a faster rate of age-related frailty than their wildtype controls. These results indicate that both 3xTgAD and 5xFAD mice show more age-related indices of frailty than their wildtype controls, which may explain the shortened lifespan of these mice.

67. **Age-related cognitive changes in 3xTg and 5xFAD mice: assessment using touchscreen-based automated tasks.** Boyer Winters1, Daniel Palmer1, Samantha Creighton1, David Wasserman1, Meghan Thorne1, Jocelyn Schubert1, Flavio Beraldo2, Talal Masood2, Matthew Cowan2, Vania Prado2, Marco Prado2**.** 1Department of Psychology and Collaborative Neuroscience Program, University of Guelph, Guelph, ON, N1G 2W1; 2Robarts Research Institute/Dept of

Physiology and Pharmacology/Dept of Anatomy & Cell Biology, The University of Western Ontario, London, ON. Traditional measures of learning and memory have contributed greatly to our understanding of cognitive functions in mouse models of Alzheimer's disease (AD). However, these tasks typically bear little resemblance to tests used for cognitive assessment in patient populations; this lack of face validity is a potential factor in the common failure to translate results from pre-clinical animal studies to clinical trials. The growing popularity of touchscreen-equipped operant boxes for cognitive assessment in rodents presents a unique opportunity to redress this issue. This approach enables relatively high-throughput testing of mice in tasks that can be modelled after human neuropsychological tests and reduces common sources of variability to facilitate cross-task comparison within and between strains. We are currently analysing age-related changes in the 3xTg and 5xFAD strains of mice using touchscreen-based operant tasks. We are focusing on a test battery consisting of the 5-choice serial reaction time test (5CSRTT) of sustained attention, visuo-spatial paired associate learning (PAL), and visual pairwise discrimination (PD). Initial results indicate attentional deficits in the 5CSRTT in male and female 3xTg mice as early as 4.5 months of age. Conversely, 5xFAD mice do not differ from wildtype controls at 4.5 months, but impairment is observed in female 5xFAD mice at 7 months. By 10 months of age both sexes within both strains are impaired. These and data from the PAL and PD tasks will be discussed in the context of their relevance to pathology and cognition in AD. The touchscreen battery approach should ultimately provide insight into the shared and non-overlapping cognitive deficits in various AD mouse models, as well as improving efforts to predict the potential for novel compounds to treat cognitive impairment in AD. Supported by the Weston Brain Institute.

68. **The role of hippocampal dopamine D2-type receptors in the social transmission of food preferences in male and female mice.** Matta, Richard1; Underwood, Emily A.1; Leach, Zoe K.1; Vertes, Alex C.1; Choleris, Elena1**.** 1Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON N1G 2W1 Canada**.** The neurotransmitter dopamine (DA) is involved in the regulation of many motivationally relevant behaviors, including drug/alcohol addiction, as well as social interactions, food intake, and social learning. With systemic treatments, our lab has previously implicated DA D1-type receptors in social learning, and DA D2-type receptors in feeding behavior in the social transmission of food preferences (STFP) paradigm in mice (Choleris et al., 2011). However, where these DA receptor families are acting in the brain to influence such behaviors in the STFP remains unknown. The ventral tegmental area has direct dopaminergic projections to many limbic structures, including the nucleus accumbens, amygdala, and the hippocampus—a site important for learning and memory processes, as well as social learning in the STFP. We have previously found that antagonizing dorsal hippocampal DA D1-type receptors blocks social learning in the STFP in both male and female mice (Matta & Choleris, 2014). In an ongoing study, we are microinfusing the DA D2-type receptor antagonist Raclopride (at 10, 14, 18 and 20 µg/µL) directly into the Cornu Ammonis 1 (CA1) region of the dorsal hippocampus of adult male and female CD-1 mice. Microinfusions are administered 10 minutes before a 30 minute social interaction, where mice have the opportunity to develop a food preference from a same-sex conspecific. Given the role that mesolimbic DA D2-type receptors play in individually acquired food preferences (e.g. Sclafani et al., 2011), it is hypothesized that hippocampal DA D2-type receptors will also play a role in socially acquired food preferences, and may also mediate food intake. This study may shed light on the importance that hippocampal DA D2-type receptors contribute to the processing of socially relevant information. Supported by NSERC.

69. Increased neuronal density in ca1, locomotion and levels of estradiol in presence of a bee products in postmenopausal rats. Mayen Díaz Rodrigo1, Vázquez Matías Daniel Aarón1, Zarraga Galindo Norma1, Sanchez Cervantes Ivonne Grisel2, López Martínez Irma2, Fragoso Alcalá Elvis2, Martinez Tapia Ricardo2 ,Velázquez Paniagua Mireya1, Ramírez Escoto Marcela 2, Vergara Aragón Patricia1**.** 1Depto de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México. 2Depto. de Biología Celular y Tisular, Facultad de Medicina, Universidad Nacional Autónoma de México. THE AIM of this research was to evaluate the correlation between serum levels of 17β-estradiol and locomotion in ovariectomized (OVX) postmenopausal (PM) rats with hippocampal neuronal density in the CA1 and CA3 areas, in presence of a mixture of bee product (BP). MATERIAL AND METHODS. Wistar PM rats (> 9 months, 600-800 g) divided into four groups were used: 1)

without oophorectomy / without BP, 2) without oophorectomy / with BP , 3) OVX rats/ without BP and 4) OVX rats/ with BP. Groups 2 and 4 received a mixture of BP, which includes honey, propoleo, royal jelly, B complex, queen bee larvae, vo , 0.2 mg / kg / 28 days. Locomotion was assessed with the open field test, 5min each day for 28 days; estradiol determination was performed by ELISA after 28 day. The hippocampal neuronal density was determined in histological sections processed with ordinary histological technique in CA1 and CA3 areas. The results were analyzed with ANOVA for one factor and Tukey test. RESULTS. In the test of locomotion to compare groups 2 and 4 (with BP) both showed a similar performance: 49.4 ± 10.48 vs 50.7 ± 13.31 ; while contrasting groups 3 and 4 (OVX rats) , group 3, without BP, showed less locomotor activity than the 4 group with BP: 37.9 ± 10.12 vs 49.4 ± 10.48 ; p = 0.004 .Serum levels of 17β -estradiol were similar in groups 1, 2 and 4: 49.1 ± 7.29 ; 48.22 ± 6.88 and 43.98 ± 5.094 pg / ml , respectively. It was also noted that the group of OVX rats receiving the BP (group 4) showed an increase in their levels of 17β -estradiol to the group that did not receive (group 3) : 43.98 ± 5.094 vs 25.700 ± 9.595; p = 0.001. Evaluation of hippocampal neuronal density showed that in the OVX groups (group 3 vs group 4) , which received the BP (group 4) rats had a significant increased neuronal population (18.136 ± 3.8 vs 35.811 ± 7.44 p= 0.01) . The effect of ovariectomy in PM rats with BP causes increased particularly in CA1 neuronal population. CONCLUSIONS. We conclude that mixture of BP administered by vo, has been related with a neuroprotective effect on hippocampal CA1 population, correlated with an increase in gross motor activity and hormonal levels analyzed. This may be due to the presence of queen bee larvae (estradiol content of which is high), honey, B complex, royal jelly and propoleo.

70. **Dissociable contributions of maintenance and de novo DNA methyltransferases to object and spatial memory in the rat perirhinal cortex and hippocampus.** Creighton, S1,2., Mitchnick, K1,2., Al-Izzi, A1., Kalisch, B3., Winters, B1,2. 1 Department of Psychology, 2Collaborative Neuroscience Program, 3 Department of Biomedical Sciences, University of Guelph, Ontario, Canada. DNA methylation, catalyzed by DNA methyltransferases (DNMT), is an epigenetic mechanism that can support cellular memory by modifying gene expression; specifically, methylated genes are not expressed and unmethylated genes are expressed. Learning induced alterations in DNA methylation may balance expression of memory promoting and inhibiting genes and are critical for mnemonic function. By inhibiting DNMT subtypes we have shown a dissociable contribution of DNMTs to object-in-place (OiP) memory in rats, such that maintenance DNMTs (DNMT1) in the perirhinal cortex (PRh) and de novo DNMTs (DNMT3a) in the hippocampus (HPC) are necessary for long-term memory. In OiP the PRh is involved in the processing of object identity and the HPC is involved in spatial processing; therefore our findings suggest that epigenetic mechanisms may not generalize to different types of memory. The present study systematically examined the unique contribution of DNMTs to object identity (object recognition) and spatial memory (object location), which are dependent on the PRh and HPC, respectively. Disruption of DNA methylation during object recognition and object location learning by administration of the non-selective DNMT inhibitor RG-108 revealed that intra-PRh DNA methylation is required for long-term object recognition and intra-HPC DNA methylation is required for long-term object location memory. Selective inhibition of PRh DNMT1 by short-interference RNA (DNMT1 siRNA), but not DNMT3a siRNA, impaired object recognition when the retention delay was 24h. Intra-HPC administration of DNMT3a siRNA, but not DNMT1 siRNA, impaired object location when the retention delay was 24h. Behavioural results are consistent with a differential contribution of maintenance and de novo DNMTs to different facets of memory processed by different brain regions. Complementary molecular analyses will explore mRNA expression of genes that regulate memory (brain-derived neurotrophic factor, reelin, protein phosphatase 1, and calcineurin) and neurogenesis (neuron differentiation 1, disrupted in schizophrenia 1, and Wnt-3) in the PRh and HPC following object and location learning. Preliminary results show an upregulation of only brain-derived neurotrophic factor in the PRh, but not HPC, following object recognition, confirming the function of the PRh and expression of memory promoting genes in this task. Supported by NSERC.

71. **Play it again, Sam: An investigation of rough-and-tumble play on neurobiological and cardiovascular markers of emotional regulation in rats exposed to repeated stressors.** Scott, S., Kent, M., Bardi, M., & Lambert, K. Department of Psychology and Behavioral Neuroscience, Randolph-Macon College, Ashland VA USA. Rough-and-tumble (RAT) play has been shown to be

an important behavior in developing mammals, with insufficient play responses linked to cognitive and emotional conditions such as Attention Deficit Hyperactivity Disorder (ADHD; Panksepp, 2007). Accordingly, the current study focused on the effect of RAT play on emotional regulation measures including learning acquisition and prediction errors in a foraging task (dry land maze; DLM) as well as responses to the repeated exposure to restraint stress and swim stress. Twenty-four newly weaned male isolate-housed Long-Evans rats were randomly assigned to one of three groups: RAT play twice daily (30 min per session; PLAY group); a social control group with barrier separating animals (SOCIAL CONTROL; SC); and a no contact control group that was deprived of play and any contact with a conspecific (NO CONTACT; NC). Following two weeks of play sessions, rats were trained in the DLM; subsequently, all animals were exposed to three days of 15-min exposure to restraint stress for cardiovascular assessment and then three days of 3-minute swim stress. Fecal samples were collected during baseline and following the first and third days of swim stress for assessment of corticosterone (CORT) and dehydroepiandrosterone (DHEA). Subsequently, the brains were processed for Neuropeptide Y- and Brain Derived Neurotrophic Factor-immunoreactivity in the amygdala and hippocampus. Results indicated that the PLAY group exhibited more focus on the DLM task during test day 3 by exhibiting significantly less general exploration and inspection of fewer wells in pursuit of the baited well. During the probe trial, the PLAY group emitted fewer fecal boli than the SC and NC groups. Cardiovascular assessment indicated that the PLAY groups were more active in the restraint tubes on the first day and had a trend toward lower systolic blood pressure compared to SC and NC groups. In the swim task, PLAY animals emitted fewer fecal boli and a trend toward more dives, indicating bolder responses, on the first swim day. Although no effects of RAT play were observed in CORT or DHEA, 62% of the PLAY animals exhibited no increase in CORT from the baseline to first swim measure, compared to 38% and 25% of the SC and NC groups, respectively. Although brain quantification is still in progress, no effects have been observed thus far. In conclusion, although learning in the DLM was observed in all groups, the PLAY group exhibited more attentional focus on the third test day and less anxiety during the probe test; PLAY animals also exhibited a few responses characteristic with emotional regulation in the cardiovascular and endocrine assessments. This research was supported by the Brock Professorship funds awarded to KGL.

72. Phenotyping emotional resilience: Flexible coping strategies align with adaptive neurobiological responses to prediction errors and challenge tasks in male and female rats. Kent, M., Hazelgrove, A., Sewell, K., Kirk, E., Thompson, B., Lambert, S., Trexler, K., Terhune-Cotter, B., Bardi, M., & Lambert, K. Department of Psychology and Behavioral Neuroscience, Randolph-Macon College, Ashland VA USA. Despite a multibillion dollar antidepressant industry, depression rates continue to rise; for example, from the 1990's to 2000's, prescription rates for antidepressants increased by 400%. These discouraging numbers have reignited interest in the identification of effective nonpharmacological approaches. Past research in our laboratory has identified predisposed coping strategies associated with emotional resilience, providing a potential buffer against the emergence of depression symptoms. Compared to more consistent active and passive coping profile groups, rats with a flexible coping phenotype exhibit neurobiological markers of emotional regulation to various acute stressors. In the current study, responses of male and female rats to prediction errors in a spatial foraging task (dry land maze; DLM) were examined after animals were exposed to a depressogenic chronic unpredictable stress protocol for two weeks. Subsequently, all animals were trained in the DLM with the target assessment being the final probe test. Brains were processed following this task for fos-activation patterns. Results indicated that males exhibited more active exploration in the DLM probe test whereas flexible and active females exhibited more strategic rear responses (targeted to interior of maze) in the absence of the predicted reward than their male counterparts. Regardless of sex, a trend for flexible copers to spend more time in proximity to the previously baited well was observed. In a conditioned fear stimulus test, males exhibited more general exploration in response to the fear-stimulus whereas females exhibited increased rear responses and interrupted grooming sequences. Fecal samples collected during baseline and following a forced swim exposure revealed higher corticosterone (CORT) in active copers, whereas flexible copers had higher dehydroepiandrosterone (DHEA) and DHEA/CORT ratios, both indications of enhanced emotional regulation. The flexible copers exhibited fewer fos-immunoreactive cells in the basolateral amygdala and a trend toward lower activation in the insula, with no differences

observed in the hippocampus and pyriform cortex. In sum, although human females are twice as likely to suffer from depression as males, sex effects weren't as pervasive as coping strategies in the neurobiological assessments of emotional regulation/resilience utilized in the current study. However, females exhibited varying behavioral strategies, suggesting that their responses may be differentially targeted toward more specific information gathering in uncertain and stressful conditions. This work was supported by NIMH award 1R15H101698-01A1 to KGL.

73. C-Fos expression of anxiolytic effects of benzodiazepines in prefrontal cortex of rats. S.E. Cruz-Morales, D. J. González-Sánchez, G. Castillo-Roberto. UNAM, FES-Iztacala, Psyichopharmacology. Chronic use of benzodiazepine anxiolytics induces tolerance and dependence. It is known that the effects of drugs could be modulated by context´s cues associated with their administration. Previously we demonstrated that the anxiolytic effects of Diazepam (D) and Midazolam (M) are dependent upon the context. Expression of C-Fos protein allows identifying the neural activation to different stimuli. The objective of this work was to analyze the effects of acute and chronic administration of M and D on different contexts. Male Wistar (200 g) were randomly assigned to independent groups and treated acute or chronically (20 days) with saline (S), 1mg/kg of M or D, in different contexts, colony room (C) or laboratory (L). Four groups received acute administration of D and M in each context (ADC, ADL; AMC, AML) and other four received the treatments for 20 days (CDC, CDL; CMC, CML). At the end of each treatment anxiety was evaluated in the elevated plus-maze (EPM). Two hours later, subjects were sacrificed; the brains removed and processed for the immunohistochemical detection of C-Fos protein. Acute administration of M and D increased the percentage of entries and time of permanence in open arms and a decreased the C-Fos expression in Cg, IL y PrL. The behavioral results after chronic administration were dependent upon the context of administration. The groups that received M and D in the same context of administration and test (CML, CDL) no differed from control group, showed tolerance; while the groups tested in different context (CMC, CDC) showed an anxiolytic effect. The groups tested in different context (CMB, CDB), showed reductions of C-Fos expression, with M significant effects were detected in Cg, IL and PrL, with D only in IL. In tolerant groups (CML y CDL) no differences were detected compared with control group. Present results are consistent with previous findings about the importance of context in C-Fos expression in PFC (Souza, 2009) suggesting its participation in the modulation of anxiety. We thank technical assistance of C. Estrada and C. Morán BUAP. Supported by UNAM, DGAPA, PAPIIT IN30771.

74. **Scorpion Venom Heat-Resistant Peptide (SVHRP) treatment rescues deficits in learning and memory of APP/PS1 transgenic model mice of Alzheimer disease.** Shao Li1, Jin-Yi Yang2, Guang Yang1, Jian-Jiao Chen1, Tao Wang1, Yan Peng1, Jie Zhao2*. 1 Department of Physiology, Dalian Medical University, Dalian, 116044, China, 2 Department of Urology, Dalian friendship hospital, Dalian.116021, China. The progressive cognitive decline of Alzheimer disease (AD) is thought to be a consequence of loss of synapses and eventually neurons in basal forebrain, cortex and hippocampus. Scorpion venom heat-resistant peptide (SVHRP), as a component purified from Buthus martensii Karsch scorpion venom, was indicated to promote endogenous neurogenesis and maturation of newly generated immature neurons in adult mice by increasing the expression of BDNF in astrocytes. These imply SVHRP could alleviate deficits in synaptic plasticity. Here, we investigate the effect of SVHRP on cognitive deficits in APP and presenilin 1 (APP/PS1) transgenic mice which express human mutant APP and PS1. APP/PS1 transgenic model mice of AD were randomly assigned into SVHRP-treated (TG+SVHRP) and control (TG) APP/PS1 transgenic mice. APP/PS1 mice, which show amyloid plaques at 3 months of age and deficits in synaptic plasticity and cognition at 7 months of age, were intraperitoneally injected with SVHRP 20 mg/kg body mass, while the control group received 5 ml/kg body mass saline, once per day at 5 months of age for 6 months. The effect of SVHRP on spatial memory was examined by using the Morris water maze test. Control APP/PS1 mice showed that learning in locating the submerged escape platform was impaired, as indicated by the increased escape latencies in the consecutive trials compared with WT mice. In contrast, SVHRP-treated APP/PS1 mice showed reduced escape latencies compared with control APP/PS1 mice but no change with swimming speed between the groups (ANOVA, $p<0.05$). SVHRP-

treated APP/PS1 mice cross the former platform location more often than control group (ANOVA, $p<0.05$). The conclusion is that chronic SVHRP treatment could rescue deficits in learning and memory of APP/PS1 mice. Acknowledgments: This work was supported by grants from the National Natural Science Foundation of China (NSFC, 81371223 and 81371437).

75. **Postnatal stress induced by injection with valproate leads to developing emotional disorders along with molecular and cellular changes in the hippocampus and amygdala.** Wang, Chih-Yen1; Wang, Wei-Hua1; Cheng, Chien-Wen1; Chen, Po-See2; Tzeng, Shun-Fen1. 1Department of Life Sciences,2Department of Psychiatry, College of Medicine, National Cheng Kung University, Tainan, Taiwan. Stress derived from adverse environment during brain development could contribute to psychiatric disorders. To study the influence of stress occurring at birth in human on behavior development, we performed intraperitoneal injection of valproic acid (VPA; 200mg/kg), a histone deacetylation inhibitor (HDACi), into male rat pup at postnatal day 7 (P7) that is comparable to infant at 36–40 week gestation. We found that neuronal differentiation genes (i.e. doublecortin and NeuroD1) and oligodendrocyte-specific transcription factors Olig1 and Oligo2 were downregulated in the hippocampus of VPA-treated rat pups. In addition, enhanced cell proliferation was observed in the hippocampus and amygdala of rats receiving postnatal VPA injection. Moreover, microglial morphological changes in the hippocampus and amygdala were rapidly induced at 24 h after a single injection with VPA. Accordingly, peripheral administration of VPA into postnatal rat pups exerted the effects on the disruption of cell proliferation and neural cell-related gene expression in the two brain regions that have been known to mediate emotional behaviors. Through several behavior tests, we found that rats receiving postnatal injection with VPA displayed depressive and anxiety-like behaviors at the late postnatal ages, and had impaired social interaction at 8-week old. In summary, our findings that postnatal injection with VPA induced anxious, depressive and impaired social behaviors, demonstrate that early life stress to infant is the great risk to develop emotional disorders in youth and its effects possibly sustains in adulthood possibly due to altered gene expression and neuron-glia interaction occurring in the hippocampus and amygdala at the early age.

76. Reversal of effect in the novel object recognition (NOR) test in the presence of an external olfactory stimuli. Alumri Talal,1-2 Greengrass Colin1-2, Zhu Yi Zhun1-2**.** 1College of Medicine, Imam Mohammed Ibn Saud Islamic University , 2College of Medicine, King Saud university, Riyadh , Kingdom of Saudi Arabia; 3College of Pharmacy, Fudan university, Shangahi, China**.** Introduction: Animal models of memory have been the subject of much scientific study. The novel object recognition (NOR) test can be evaluated by the differences in exploration time of novel and familiar objects and represents more complex learning. Several studies have indicated the potential of the NOR test in representing cognitive activity in rodents, however, in this study we found a reversal of effect in the presence of external stimuli. Objectives: To determine the relationship between cognitive activity and novelty preference in rodents in the presence of an external olfactory stimuli in NOR. Material & Methods: Effects of an external olfactory stimulus on behavior in the NOR test were studied using 36 Wistar rats divided into 3 treatment groups consisting of 12 animals, 6 males and 6 females, housed separately. All groups followed the NOR protocol, Group A acted as a control group without exposure to olfactory stimuli. Group B was exposed to an olfactory stimuli in their home cage and testing environment, while Group C was exposed to an olfactory stimuli throughout the training and testing environment. Results: Within the testing phase significant differences were observed as an increased exploration at the familiar object in groups B and C compared to controls, and in group C a significant increase in exploration at the familiar object compared to the novel object, which is a reversal of the effect observed in controls and of that found in published studies. Conclusions: The concept of the NOR paradigm is based on the concept of novelty, assuming rats spend more time with a novel object than a familiar object. In this study animals exposed to an olfactory stimuli appear to prefer to explore or spend time at the familiar object.. However these findings may drawing a questions to the validity of this test to measure higher cognitive function , Underlying mechanisms and ideas for further research are also suggested.

77. **Fear and fear extinction learning in APP/PS1 mice.** Thomas Endres1, Gloria Hölzl1, Alican Caglayan1, Volkmar Lessmann1,2, Elke Edelmann1**.** 1Institute of Physiology, Otto-von-Guericke University, Magdeburg, Germany**.** 2Center for behavioral brain sciences (CBBS), Otto-von-Guericke

University, Magdeburg, Germany**.** One of the most challenging topics in neuroscience research is the identification of novel treatment approaches for Alzheimer's disease (AD). It has been shown by several studies, that in AD patients emotional processing, e.g. the recognition of fearful faces or the learning of fear, is impaired. Interestingly, these impairments occur already at early stages of the AD etiopathology. Thus, an altered emotional processing might be regarded as an early symptom in the development of AD. In the present study, we analyzed different aspects of fear learning and fear extinction in differently aged APP/PS1 mice. This AD mouse model combines the Swedish APP (KM670/671NL) mutation with the PS1-L166P mutation under control of the Thy1 promoter (Radde et al., 2006, EMBO), resulting in a rather mild but constant post-developmental expression of Aβ and subsequent plaque formation. By testing amygdala-dependent cued fear learning, we observed only slight impairments in 12 months old but not in younger APP/PS1 mice. In the adjacent fear extinction training, we observed no impairments in the extinction of these cued fear memories, neither in short nor in long-term extinction memory. In contrast to the cued fear learning, we observed deficits in contextual fear learning in six months old APP/PS1 animals. Here, animals could not discriminate between the conditioned and a neutral context. However, the subsequent extinction of these contextual fear memories seemed to be unimpaired. Currently, we are analyzing the protein level of Aβ40/42 in the hippocampus, amygdala and medio-prefrontal cortex of the tested animals in order to correlate the local occurrence of these toxic Aβ-species with the behavioral performance of the animals. In addition, we started to analyze long-term potentiation (LTP) in acute hippocampal slices from APP/PS1 mice. Here, first results indicate an impaired LTP in the CA1 region of six but not three months old APP/PS1 mice. In conclusion, we could demonstrate selective impairments in contextual fear learning in middle-aged APP/PS1 mice. Experiments trying to further analyze the underlying mechanisms for this deficit by analyzing expression levels of soluble forms of Aβ protein and altered hippocampal synaptic plasticity are in progress. This work was supported by the Center for behavioral brain sciences (CBBS) and the Deutsche Forschungsgemeinschaft (DFG, SFB 779/B6).

78. **A glycine receptor subunit homologue, avr-14, alters short-term memory in an interstimulus interval-dependent manner in c. Elegans.** McDiarmid, Troy A.1, Adriel, Evan L.1, Rankin Catharine H.1. 1University of British Columbia Brain Research Centre. Habituation is a learned decrement in response following repeated exposure to a stimulus that cannot be explained by sensory adaptation or fatigue. Despite its importance, the mechanisms underlying habituation remain largely unknown. Repeated exposure to taps (non-localized mechanosensory stimulation) leads to habituation of a reversal withdrawal response in C. elegans that is dependent on glutamate transmission and postsynaptic AMPA receptors. Here we use high throughput behavioural analysis to characterize the role of AVR-14, an inhibitory glutamate gated chloride channel homologous to vertebrate glycine subunits. avr-14 loss of function mutants display a larger initial reversal duration in response to tap and faster habituation to tap stimuli than wild-type animals at a 10s interstimulus interval (ISI). At long ISIs (60s), avr-14 mutants habituated significantly less than wild-type animals. The stark contrast in phenotypes at short and long ISIs necessitated analysis of habituation across ISIs (10-60s ISIs). This revealed that mutations in avr-14 result in faster habituation at short ISIs, wild-type habituation at intermediate ISIs, and slower habituation at longer ISIs. Together these studies suggest mutations in avr-14 alter habituation in an ISI-dependent manner. Experiments using cell-specific knockdown, rescue, and stimulation will localize the memory functions of AVR-14 to elucidate how it modulates the tap habituation circuit. These studies will determine how the inhibitory functions of glutamate mediate short-term habituation in C. elegans, furthering our understanding of the processes underlying learning and memory.

79. **Prenatal alcohol exposure increases anxiety-like behavior in males but depressive-like behavior in females two weeks following chronic unpredictable stress.** Vivian Y.Y. Lam1, Lily Takeuchi1, Charlis Raineki1, Joanne Weinberg1. 1Department of Cellular and Physiological Sciences, The University of British Columbia, Vancouver, Canada. Depression and anxiety are often associated with stress, with symptoms developing sometimes weeks or months following cessation of stress. However, stress per se may not be sufficient to cause depression or anxiety, but it may be more potent in the context of a biological predisposition. Prenatal alcohol exposure (PAE) is known to cause long-term hypothalamic-pituitary-adrenal hyperresponsivity to stressors, and may thus increase sensitivity to the adverse effects of stress. Indeed, PAE appears to increase the risk of developing

depression and anxiety in adulthood. To better understand the effects of the interaction between prenatal alcohol exposure and later life stress on mental health, this study examined how prenatal alcohol exposure affects the immediate or delayed depressive- and anxiety-like behavioral response to chronic unpredictable stress (CUS) in adulthood. Adult offspring of alcohol-fed (PAE), pair-fed (PF), and ad libitum-fed control (C) dams were either exposed to 10 days of CUS or left undisturbed. Behavioral testing began 1 or 14 days post-CUS (CUS-1 and CUS-14, respectively). Anxiety-like behaviors were assessed in the light-dark emergence and elevated plus maze (EPM) tests; behavioral despair was assessed in the Forced Swim Test (FST). In the emergence test and EPM, PAE males (with or without CUS) spent less time in the lit compartment and a lower % time in the open arms than C, and only PAE males in the CUS-14 group emerged later and performed stretch-attend behavior less frequently than CUS-14 controls. In contrast, females showed no differences in the emergence test and CUS decreased PAE females' stretch-attend frequency in the EPM to control levels. In the FST, CUS decreased immobility time across all male groups. In females, immobility time increased in all females when tested immediately following CUS. Importantly, this increase persisted after two weeks, but only in PAE females. Overall, PAE males appear to show higher anxiety than controls as well as increased sensitivity to the delayed anxiogenic effects of CUS, while PAE females appear to show increased sensitivity than controls to the delayed depressogenic effects of CUS. These results suggest that prenatal alcohol exposure alters, in a sexually-dimorphic and time-dependent manner, anxiety- and depressive-like behavior following CUS exposure. Support: NIH/NIAAA R37 AA007789 and RO1 AA022460, and NeuroDevNet to JW; CFFAR to JW and CR; and NSERC PGSD and IMPART to VL.

80. **Effects of osmotic and non-osmotic stimuli on drinking behavior in trpv1 and trpv4 knockout mice.** Yoichi Ueta1, Takanori Matsuura1,2, Yasuhito Motojima1,2, Mitsuhiro Yoshimura1, Kanako Shoguchi1, Takashi Maruyama1, Hirofumi Hashimoto1, Makoto Kawasaki2, Hideo Ohnishi2 and Akinori Sakai2**.** 1Department of Physiology and 2Orthopaedics, School of Medicine, University of Occupational and Environmental Health, 807-8555 Japan. It is possible that the detection of plasma osmolality and body fluid volume and sensation of thirst related to drinking behavior may be mediated in part by products of the genes encoding the transient receptor potential vanilloid 1 (TRPV1) and TRPV4 channels. The purpose of the present study was to examine the effects of osmotic and non-osmotic stimuli that cause drinking behavior on water intake in TRPV1 knockout (TRPV1-/-) and TRPV4 knockout (TRPV4-/-) mice in comparison with wild type (WT). Intraperitoneal injection of hypertonic saline (HS) (1.0M NaCl, 2% of body weight) and water deprivation (WD) for 24 hours was performed as osmotic stimuli. Subcutaneous injection of 20% polyethylene glycol (PEG) (MW 4,000) (0.2 mL/10g body weight) and intracerebroventricular injection of angiotensin II (AII) (200 ng per mice) was also performed as non-osmotic stimuli. PEG was used as non-osmotic but hypovolemic stimulation. After osmotic and non-osmotic stimuli, accumulating water intake from 0 to 24 hours (48 hours in some case) in each mouse was measured in metabolic cage. HS and WD caused drinking behavior and drank similar accumulating water volume in all types of mice. PEG-induced water intake in TRPV4-/- mice was significantly smaller than that in TRPV1-/- and WT mice (there was no different water intake between TRPV1-/- and WT). AII-induced water intake in TRPV1-/- mice was significantly smaller than that in TRPV4-/- and WT mice (there was no different water intake between TRPV4-/- and WT). These results suggest that TRPV1 and TRPV4 may be involved potently in AII- and hypovolemia-induced drinking behavior, respectively.

81. **Activation of Adenosine A2A receptors exacerbates cognitive dysfunction induced by traumatic brain injury by promoting hyperphosphorylation of the C-terminal of Tau protein.** Yuanguo Zhou1, Ziai Zhao1, Ping Li1, Yalei Ning1, Nan Yang1, Yan Peng1, Yan Zhao1, Xingyun Chen1, Xing Chen1, Wei Bai1, Xujia Zeng1**.** 1Molecular Biology Center, State Key Laboratory of Trauma, Burn, and Combined Injury, Research Institute of Surgery and Daping Hospital, Third Military Medical University, Chongqing, China**.** Adenosine A2A receptor (A2AR) is activated during traumatic brain injury (TBI) and involved in cognitive impairment particularly in learning and memory. Tau is a microtubule-associated protein, and its function is influenced by phosphorylation, which is significantly increased in cognitive dysfunction with neurotrauma and neurodegeneration. However, it is not known whether A2AR activation exacerbates cognitive impairment via promoting Tau protein's hyperhosphroylation. In this study, in a moderate controlled cortical impact model of mice, we found

tau protein's phosphorylaytion level at Ser404 site in injuried hippocampus significantly increased compared with the sham group after TBI. Morever, we found that A2AR antagonist ZM241385 or A2AR knock out significantly reduced the phosphorylation level of tau at Ser404 site in dentate gyrus region and alleviated the reference and working memory dysfunction at 7d and 4w post TBI. Meanwhile, selective A2AR agonist CGS21680 significantly increased tau protein's phosphorylation at Ser404 site and impaired reference and working memory after TBI. To further investigate whether A2AR could affect tau protein's phosphorylaytion, we found that CGS21680 promoted tau protein's phosphorylation at Ser404 site in cultured primary hippocampal neurons, as well as a significant decrease of the number of axonal mitochondrion compared with the control group. And this effect was associated with PKA and GSK-3beta activation. Furthermore, A2AR antagonist ZM241385 can reverse this effect. Our findings provide an important experimental evidence to elucidate a new mechanism of cognitive dysfunction induced by the activation of A2AR through increasing the phosphorylation level of tau proteins after TBI and a promising therapeutic and prophylactic strategy.

82. **Lutein dietary supplementation inhibited the oxidative and inflammatory biomarkers in the brain of diabetic rats.** Khaled A. Al-Hosaini1*, Abdulaziz S. Alroujaee2, Abdulaziz Y. Alturki3, Amal J. Fatani1**.** 1Department of Pharmacology and Toxicology, College of Pharmacy; KSU, 2Imam University 3King Khalid Univ. Hospital, KSU, Riyadh, Saudi Arabia**.** Background and Aims: Diabetes, a chronic metabolic disorder, has assumed epidemic magnitudes and its long-term complications can have devastating consequences like inducing oxidative stress. Brain is especially vulnerable to oxidative damage as a result of its high oxygen consumption rate, abundant lipid content, and relative paucity of antioxidant enzymes as compared to other tissues. Lutein is believed to be a strong antioxidant, as it protects cells from oxidative damage. In this study, we expounded the hitherto unknown potential of lutein to ameliorate the brain damage caused by diabetes mellitus and the associated hyperglycemia-induced oxidative damage. Methods: Diabetes was induced using a single IP injection of streptozotocin (STZ). Lutein content diets (40, 80 and 160 mg/kg diet) was prepared in pellet form and supplemented to diabetic rats for 5 weeks. Thiobarbituric acid reactive substances (TBARS), total sulfhydryl groups (T-GSH), non-protein sulfhydryl groups (NP-SH), superoxide dismutase (SOD) and catalase (CAT) activities were measured in brain. Pro-inflammatory mediators like tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and interleukin-6 (IL-6) were also estimated in brain cells. Cytotoxicity of brain cells was measured by estimating nucleic acids and total protein (TP) levels. Results: Lutein significantly inhibited the diabetic induced increased in brain levels of TBARS, TNF-α, IL-1β and IL-6 in dose dependent manner. Diabetes caused inhibition in levels of T-GSH, NP-SH, DNA, RNA and TP was significantly increased in lutein dietary supplemented diabetic rats compared to normal diet fed animals in dose dependent manner. Conclusion: These findings suggest that lutein has the potential to ameliorate STZ-induced damage in the brain probably through its antioxidant and anti-inflammatory properties.

83. **Stress increases sucrose intake in binge eating prone female rats.** De Avila Camila, Calvez Juliane, Timofeeva Elena. CRIUCPQ, Faculty of Medicine, Department of Psychiatry and Neuroscience, Laval University. Background: Stress appears to be one the most important among the environmental factors affecting feeding. Individual differences exist and while some people decrease their intake when stressed other eat food - especially pleasurable and high calorie food. Women are especially susceptible to emotional and stress induced eating. While these individual differences may be related to individual differences in stress reactivity, the mechanisms underlying such behaviors are not well understood and pertinent models of stress-induced binge eating are missing. Objective: The goal of this study was thus to develop and test a model in which stress induces binge eating in a subpopulation of sensitive female rats and to study the activity of stress axis. Methods: Forty adolescent female rats were included at the beginning of the study. Every rat had intermittent access (3 times per week) to 10-% sucrose during 1h at the beginning of the dark phase. Once sucrose intake got stable, rats were submitted to foot shock stress sessions and immediately after exposed to 1-h sucrose. Rats were then categorized as binge eating prone (BEP) and binge eating resistant (BER) based on the amount and consistency of sucrose intake across feeding tests after stress sessions. Plasma corticosterone levels in control condition and after stress were determined. Results: On 40 rats, 33% were classified as BEP rats (n=12) and 33% were classified as BER (n=12). BEP presented an increased sucrose intake compared to BER in both control (P=0.001) and stress

conditions (p<0.0001). Furthermore, BEP rats showed higher intake of sucrose after stress compared to their control intake without stress (p<0.0001) whereas no difference between sucrose intake in control condition and after stress was found in BER rats. Additionally, BER group decreased their daily food intake after stress (P=0.0112) and no effect of stress was observed on daily intake in BEP rats. Plasma corticosterone was increased after stress in BER group (P=0.0228) while BEP group displayed a blunted corticosterone response following acute stress. Conclusion: In our model, stress induced an increase of sucrose intake in BEP rats. This binge eating behavior was accompanied by a dysfunction of the stress axis which may explain the blunted anorectic effect of stress in this group. This model can now be used to identify the unique neuronal mechanisms underlying these two phenotypes and suggest more specifically targeted treatments for binge eating.

Thursday, June 4

8:00-10:00 Neuroadaptations to chronic antipsychotic treatment in preclinical models.
Chair: Anthony Vernon, Margret Hahn.

Presynaptic adaptations associated to a gradual loss of antipsychotic efficacy. Davide Amato**.** Department of Psychiatry and Psychotherapy, University Hospital Erlangen, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany**.** Treatment failure-after initial success is a key cause of relapse in schizophrenia. The neurobiological bases of treatment failure are unknown. We translated antipsychotic failure in animal models. In rodents, antipsychotic treatment failure appears already after 2-3 weeks treatment depending on treatment modality. This treatment outcome in humans and animals is normally interpreted as a consequence of dopamine supersensitivity, due to an upregulation of dopamine D2-type receptors. However, data not always have proved it to be the case. We suggest that chronic treatment with antipsychotic drugs leads to a depletion of cortico-striatal basal dopamine levels via increased clearance activities. Reduced basal dopamine levels impair homeostatic negative feedback mechanisms, which normally prevent excessive dopamine release upon stimulation. This adaptation would cause dopamine supersensitivity - independently of D2 receptor level changes. We addressed this hypothesis using several neurobehavioural methods and found evidence for neuroplasticity associated with preclinical antipsychotic efficacy and failure, which has the potential to provide insight to aid our understanding of antipsychotic failure in the clinic.

Impact of chronic antipsychotic drug treatment on brain morphology: a cause for concern? Dr. Anthony Vernon1. 1King's College London, Institute of Psychiatry, Psychology and Neuroscience, Department of Basic and Clinical Neuroscience, London, UK. Progressive loss of grey and white matter has been linked to the pathogenesis and lack of clinical improvement in schizophrenia (SCZ) and related psychoses. Increasing evidence from neuroimaging and neuropathology studies however, suggests that chronic antipsychotic treatment may contribute to the trajectory of brain volume decreases. Therefore it is critical to differentiate "disease" from "medication"-related brain volume changes and determine the underlying biological mechanisms. Addressing these questions in clinical populations is challenging. Ethical issues preclude a definitive study of placebo-treated SCZ patients and healthy individuals chronically treated with antipsychotics. Furthermore, neuroimaging findings in humans cannot easily be confirmed by neuropathology. Rodent models offer an effective means to address some of these issues, affording precise control over drug exposure, age, and linking in vivo neuroimaging with ex vivo neuropathology. Therefore, we have implemented a model in laboratory rats combining serial in vivo MRI (clinically comparable technology) and clinically relevant antipsychotic doses with post-mortem analysis, to link in vivo neuroimaging findings with neuropathology. This work has demonstrated that in normal animals, chronic antipsychotic treatment decreases total neocortical volume1, an effect seen across different antipsychotics (Haloperidol and olanzapine)1, distinct from what is seen with chronic lithium2 and is reversible on drug withdrawal2. Our most recent work has demonstrated that antipsychotics specifically reduce the volume and thickness of the anterior cingulate cortex (ACC) but not that of the primary visual (V1) cortex. Decreased ACC volume is associated with no significant loss of either neurons or astrocytes, but rather, an increase in the density of these cells3, accompanied by significant microglial activation. These data suggest the drug-induced changes are likely to reflect alterations in synaptic or

dendritic architecture, possibly mediated by microglia. This work has translational relevance to human neuroimaging studies of psychiatric illness treated with antipsychotics, including SCZ. In particular, this approach facilitates “reverse-translation”, potentially informing the neurobiological mechanisms underlying antipsychotic drug-induced volumetric abnormalities reported from neuroimaging studies in SCZ patients. Furthermore, this work may ultimately, may inform the clinical use of these drugs. References: 1. Vernon et al., Biol Psychiatry. 2011; 69(10): 936-44. 2. Vernon et al., Biol Psychiatry. 2012; 71(10): 855-63. 3. Vernon et al., Biol Psychiatry. 2014; 75(12):982-90.

Preclinical modeling of antipsychotic-related metabolic side-effects: a viable approach? Hahn, Margaret1,2,3; Chintoh, Araba1,3; Giacca, Adria4; Mann, Steve1; Remington, Gary1,2,3**.** 1Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario, Canada M5T 1R8**.** 2Institute of Medical Science, University of Toronto, 1 King’s College Circle, Toronto, Ontario, Canada M5S 1A8 3Department of Psychiatry, University of Toronto, 250 College Street, Toronto, Ontario, Canada M5T 1R8. 4 Department of Physiology, University of Toronto, 1 King’s College Circle, Toronto, Ontario, Canada M5S 1A8. Antipsychotic medications, the cornerstone of treatment for schizophrenia, have been associated with significant metabolic side effects, including dyslipidemia, weight gain and glucose dyregulation. In turn, these factors are understood to contribute to increased cardiovascular (CV) morbidity and premature mortality observed in serious mental illnesses. Understanding underlying mechanisms of these adverse effects is imperative to developing targeted interventions to attenuate cardiometabolic risk factors, and effective antipsychotic treatments devoid of these side-effects. In this respect, the field has turned to in vivo work in animals to model what is observed clinically and elucidate possible underlying mechanisms of antipsychotic-induced metabolic disturbances. As will be discussed, rodents serve as useful models for some, but not all aspects of metabolic side-effects. Weight gain, for example, is not adequately modeled, where as visceral adiposity, a major CV risk factor appears to be. Glucose dysregulation, which can occur through both adiposity-dependent, and adiposity–independent pathways, may arguably offer the strongest translational value from rodents to humans. This talk will review what we have learned from preclinical models of antipsychotic-induced metabolic dysregulation, focusing on glucose dysregulation, plausible underlying mechanisms, including our group’s recent work elucidating the role of receptor binding profiles of antipsychotic medications, and contributions of the central nervous system (CNS) to these perturbations. Discussion will also turn to using preclinical models to development of effective, targeted interventions to attenuate these side-effects.

Post-mortem studies in schizophrenia: accounting for antipsychotics. Clare L. Beasley. University of British Columbia, Vancouver, BC, Canada. While the pathophysiology of schizophrenia is not yet fully understood, post-mortem investigations have played a useful role in determining the nature of cellular and molecular alterations. Our previous post-mortem studies have identified changes in several processes, including synaptic, glial and metabolic function, in this disorder. In particular, we have reported a decrease in synaptic proteins, but higher SNARE complex formation, indicative of increased interaction between synaptic proteins. In addition, we note that the proportion of activated microglial cells and expression of the astrocytic protein GFAP are increased in grey matter, but not white matter. Furthermore, our proteomic studies indicate that energy metabolism may be dysregulated in this disorder. Second-generation antipsychotics are typically the first choice for the treatment of schizophrenia, however, it is clear that these drugs have effects on brain structure and function and as such are likely to be major confounding factors in post-mortem studies. In this presentation I will summarise our post-mortem findings in these areas and discuss the potential influence of antipsychotic medications on these data.

8:00-10:00 **Neurogenesis: Sex, drugs and memory – what’s neurogenesis have to do with it?**
Chairs: **Brian Christie, Liisa Galea.**

Stress-dependent functions for adult hippocampal neurogenesis in learning and memory. Timothy O’Leary & Jason Snyder. Department of Psychology, University of British Columbia. The discovery that new neurons are born in the adult brain has opened the door to exciting possibilities by which experience can sculpt circuits and modify behavior. In the hippocampus of adult rodents and humans, thousands of new neurons are added each day even in old age. Physiologically, immature neurons are more plastic than pre-existing neurons and there is evidence that they make functional contributions to memory.

However, the data are conflicted and their exact role remains unclear. Relatively isolated from cognitive studies of adult neurogenesis is a large body of work indicating that newborn neurons regulate emotional behaviors in response to stress. Since stress critically modulates learning, we are interested in the possibility that functions for new neurons in memory are similarly dependent upon stress. Since males and females differ in stress reactivity, we are also examining sex differences in the function of adult neurogenesis. Using a variant of the water maze where stress levels are controlled by manipulating the water temperature, we find that neurogenesis-deficient male rats indeed have impaired spatial learning and memory particularly at cold, stressful temperatures. In contrast, female rats that lack neurogenesis actually show improved performance under highly stressful conditions. Our findings are consistent with previous work showing that chronic stress, which also reduces adult neurogenesis, impairs spatial learning in males but enhances learning in females. Collectively, these data suggest that neurogenesis plays a critical role in learning under stress and performs distinct functions in the male and female brain.

The impact of sex, drugs and heavy metal on adult hippocampal neurogenesis. Richard H. Dyck1,2,4, Michael J. Chrusch3,4, Jacqueline Boon1,4, Simon Spanswick1,4, Haley Vecchiarelli3,4 and Matthew N. Hill2,4**.** 1Departments of Psychology, 2Cell Biology & Anatomy, 3Neuroscience, and 4The Hotchkiss Brain Institute; The University of Calgary. A large number of glutamatergic neurons in the mammalian forebrain sequester zinc into synaptic vesicles in their axon terminals. Synaptic zinc is released from these terminals in a calcium- and activity-dependent manner, whereupon it can exert a potent effect on neuronal signaling. A role for zinc in modulating synaptic plasticity has been inferred, but whether zinc has a particular role in experience-dependent plasticity has yet to be determined. Levels of synaptic zinc are especially high in the hilus of the dentate gyrus, one of the few sites that exhibits neurogenesis in the adult brain. We tested the hypothesis that synaptic zinc is important for modulating the level of neurogenesis by exposing ZnT3 knockout mice, which lack synaptic zinc, and wildtype littermates, to two manipulations that are known to regulate adult hippocampal neurogenesis – environmental enrichment or chronic fluoxetine treatment. Neurogenesis was assessed three- (proliferation) or six–weeks (survival) after treatment by quantifying BrDU incorporation and/or Ki67 staining. We also assessed these mice in behavioural tasks sensitive to hippocampal function. We found that the levels of neuronal proliferation and survival were not different in wildtype and knockout mice raised in standard housing conditions or receiving drug vehicle treatment. Consistent with what has been shown previously, wildtype mice exhibited significantly increased levels of neuronal proliferation and survival following exposure to environmental enrichment or fluoxetine. ZnT3-knockout mice, however, showed no enhancement in neuronal proliferation or survival after either treatment condition. Furthermore, we found that the behavioural benefits that are normally induced by environmental enrichment or fluoxetine are ablated in ZnT3-knockout mice. These data implicate synaptic zinc as an essential modulator of hippocampal neurogenesis, acting upstream of the effects of environmental enrichment and fluoxetine exposure. Supported by grant funding from NSERC and CIHR awarded to RHD and MNH.

Stressed and Depressed: How sex modifies the relationship to hippocampal neurogenesis. Liisa A.M. Galea University of British Columbia**.** Women are more likely to suffer from stress-related disorders than men, particularly during the reproductive years. Gonadal hormones, such testosterone and estradiol, play a significant role in stress-related disorders. For example, depression is more common in men with lower levels of testosterone and depression is more common in women during periods of low estradiol, such as the postpartum. However, very little research has been done to examine why these populations of men and women are more vulnerable to develop depression. Importantly, the hippocampus is vulnerable to the effects of stress and is implicated in depression; depressed patients have a small hippocampus which is related to the duration of disease. Furthermore antidepressant use by depressed patients appears to mitigate the reduction in hippocampal volume, and more so in women. Findings from our laboratory suggest that women using antidepressants have a greater increase in neurogenesis than men using antidepressants. In addition, animal models of depression, including our own, show reduced neurogenesis and synaptic plasticity in the hippocampus. We have developed specific animal models of depression that examine the effects of sex and steroid hormone differences in the vulnerability to develop depressive-like phenotypes and the relationship to neurogenesis in the hippocampus. We have created two animal models of postpartum (PPD) based on steroid hormones. In both models, either ovarian hormone withdrawal or high corticosterone postpartum, increased depressive-like behavior and reduced

neurogenesis. Furthermore reducing androgens in males also increased depressive-like behavior and reduced neurogenesis in response to stress. Together these studies suggest an important role for sex and sex hormones to modulate hippocampal neurogenesis and depressive-like behaviours and may help to better understand sex dependent vulnerabilities to stress-related disorders. Funding Coast Capital Depression Fund to LAMG.

Ambient temperature influences the neural benefits of exercise. J. Leigh Leasure1,2, Mark E. Maynard1, Chasity Chung1, Ashley Comer1, Katharine Nelson1, Jamie Tran1, Nadja Werries1, Emily A. Barton1, Michael Spinetta3. 1 Department of Psychology, 2 Department of Biology & Biochemistry, University of Houston, Houston, TX 77204**.** 3Department of Psychology, Seattle University, Seattle, Washington 98122**.** Exercise has numerous neural benefits, but many of them take weeks to manifest. It would be useful to pinpoint simple means by which to accelerate these neural benefits, including hippocampal neurogenesis, which has been linked to learning and memory. Exercise represents a significant challenge to the brain because it produces heat. Brain temperature does not rise, however, when exercise is performed in the cold. The present study was conducted in order to test the hypothesis that voluntary exercise in cold ambient temperature would stimulate hippocampal neurogenesis more so than exercise at room temperature or in hot ambient conditions. Adult female rats were given access to exercise wheels 2 hours per day for 5 consecutive days at either Room (20°C), Cold (4.5°C) or Hot (37.5°C) ambient temperature. Animals received daily injections of BrdU, in order to label dividing hippocampal precursor cells. All animals were sacrificed after exercise on the last day of the experiment. Brains were immunohistochemically processed for dividing cells (Ki67+ or BrdU+) and new neurons (assessed by doublecortin, DCX) in the hippocampal dentate gyrus. Animals exercising at Room temperature ran significantly farther than animals exercising in Cold or Hot conditions (Room 1490 + 400 meters; Cold 440 + 102 meters; Hot 291 + 56 meters). Thus, we analyzed the number of Ki67+, BrdU+ or DCX+ cells normalized for shortest distance run. Contrary to our hypothesis, rats that exercised in either the Cold or Hot conditions generated significantly more Ki67+, BrdU+ and DCX+ cells compared to rats that exercised at Room temperature. Thus, a limited amount of running in either cold or hot ambient conditions generated more new cells than a much greater distance run at room temperature. Taken together, our results suggest a simple means by which to augment the neural benefits of exercise, while minimizing exercise time.

10:30 **Keynote: Jaak Panksepp**, Bowling Green State University, Bowling Green, OH, USA. Affective neuroscience psychiatric perspectives on primal emotional feelings in other animals: Are their affects homologous to our own?

Affective Neuroscience Psychiatric Perspectives on Primal Emotional Feelings in Other Animals: Are Their Affects Homologous to Our Own? Jaak Panksepp1, Department of Integrative Physiology and Neuroscience, College of Veterinary Medicine, Washington State University. Pullman, WA 99162. Because of its bipolar positive and negative valenced structure, raw emotional feelings are an optimal way to make scientific progress on the neural constitution of emotional-affective consciousness. Such research has revealed the existence of profound neuroanatomical and neurochemical homologies in the systems that control emotionality across mammalian and avian species: Namely, wherever in their brains one applies localized Deep Brain Stimulation (DBS) and obtains coherent instinctual emotional behavior patterns, animals treat these within-brain state shifts as 'rewarding' and 'punishing' in various simple learning tasks. Humans consistently report desirable and undesirable affective changes to such DBS. These effects serve as gold prelude for the detailed neuroscientific study of affective qualia in animal and human brains. Abundant convergent evidence indicates that various “instinctual” subcortical neural networks generate homologous emotional feelings in all mammals. This knowledge allows neuroscientists to understand how brains generate affective states across species (i.e., “hard problems” of consciousness). Such work clarifies brain systems that promote psychiatric disorders, which can promote development of new mind medicines. Three anti-depressant concepts clarified by such work will be summarized (see, Panksepp, et al., 2014, Clinical Psychological Science, 2, pp 472-494) Thus, progressive understanding of the evolutionary infrastructure of cross-species subcortical emotional

networks can illuminate the affective origins of our own minds, and thereby promote new and more effective psychiatric therapeutics.

1:00-3:00 **Understanding the mechanism of behavioral flexibility and its role in cognition and abnormal behavior.** Chair: **Jennifer Catuzzi.**

Translational approach to understanding behavioral inflexibility in autism. Higher order restricted interests and repetitive behaviors are characterized by a rigid adherence to a rule or routine in autism spectrum disorders (ASD). We tested the hypothesis that behavioral flexibility impairments in ASD result from a heightened dependence on positive reinforcement and increased salience unpredicted non-reinforcement. To understand the cognitive and neural substrates that underlie behavioral inflexibility in ASD, we developed probabilistic learning tests that could be applied in both clinical and preclinical studies. Because most cases of ASD are idiopathic or polygenic, we chose to examine behavioral flexibility in BTBR mice, an idiopathic model of autism. Two-choice spatial discrimination tests were used in which a 'correct' stimulus location was reinforced randomly on 80% of correct responses and 20% for 'incorrect' responses. After learning criterion, the reinforcement contingencies were reversed. Both ASD individuals and BTBR learned the initial discrimination similar to controls, but were impaired on reversal learning. The probabilistic reversal learning deficit in both ASD individuals and BTBR resulted from an inability to maintain the new correct choice. Recent findings indicate that increased 5HT2A receptor signaling may contribute to certain ASD features. In different studies we have explored whether treatment with a 5HT2A receptor antagonist alleviates behavioral flexibility deficits in BTBR mice and whether altered 5HT2A receptor signaling in the dorsomedial striatum contributes to the behavioral inflexibility. Systemic treatment with the 5HT2A receptor antagonist, M100907, alleviates the probabilistic reversal learning deficit in BTBR. Further, direct infusion of M100907 into the dorsomedial striatum alleviates the behavioral flexibility impairment in BTBR mice. The findings suggest that altered striatal function in ASD may contribute to behavioral inflexibility in the disorder and that treatment with a 5HT2A receptor antagonist may be effective in alleviating behavioral flexibility deficits in ASD.

Effect of anxiety on spontaneous activity of the prefrontal cortex and its neuronal correlates of the extra-dimensional set-shifting. Moghaddam B, Park JC**.** University of Pittsburgh. Anxiety compromises cognitive flexibility presumably through disrupting prefrontal cortex (PFC) function. Little is known about the impact of anxiety on PFC neuronal encoding of flexible decision making. We used a clinically substantiated anxiogenic treatment to induce sustained anxiety in rats and recorded from dorsomedial PFC (dmPFC) and orbitofrontal cortex (OFC) neurons while they performed a task that required flexible switches between rules in sensory and spatial dimensions. Anxiety suppressed spontaneous activity of subpopulations of dmPFC and OFC neurons but for the most part behavioral performance and encoding of task events remained unaffected. The exception was when a previously correct sensory cue was presented as a conflicting incorrect choice. Animals displayed impaired shifting ability that was associated with reduced dmPFC encoding of conflicting cues selectively at the time of action. We propose that a neuronal substrate of the cognitive deficits of anxiety is diminished recruitment of dmPFC neurons that encode conflict related actions.

Shifts in prefrontal cortical excitatory/inhibitory dynamics in aging: implications for cognition. The ability to flexibly modify one's responses in the face of changing environmental contingencies is essential for adaptive behavior. A loss of behavioral flexibility can accompany the normal aging process but the critical neural alterations that mediate such deficits remain poorly understood. While experimental manipulations that model schizophrenia demonstrate that shifting prefrontal cortical excitatory (E) and inhibitory (I) signaling dynamics can negatively impact behavioral flexibility, less is known regarding how these signaling systems change across the lifespan. Recent work indicates that aging is accompanied by structural, biochemical and electrophysiological changes in the prefrontal cortex that mediate alterations in E/I signaling and that may confer deficits in behavioral flexibility. Biochemical analyses rats show that medial prefrontal cortical NMDA and GABA(B) receptor expression declines in aging. Further, stereological studies reveal marked, but subpopulation-specific, reductions in prefrontal cortical

interneuron number in aged rats. This reduction in interneuron number is accompanied by alterations in interneuron activity as assessed using whole-cell patch clamp electrophysiology in acute prefrontal slices from young and aged rats. Finally, acute intra-prefrontal cortical administration of the GABA(B) receptor agonist baclofen enhances aged rat performance on an attentional set-shifting task that assesses behavioral flexibility. Together, this body of work suggests that aging can result in a shift in prefrontal cortical E/I dynamics toward a hyperexcitable phenotype, which may contribute to impaired behavioral flexibility. These data will be discussed within the context of individual differences in the effects of age on prefrontal cortical-dependent cognition. Supported by AG029421 (JLB), McKnight Brain Research Foundation and NSF DGE-0802270 (SB).

Exercise effects on behavioral flexibility and prefrontal cortex in adult and adolescent rats. John T. Green, & Meghan C. Eddy. University of Vermont. Our lab has shown that voluntary exercise in adult rats facilitates learning in the first phase (Set 1) of a set-shifting task in a T-maze but not in the extra-dimensional set-shift phase (Set 2). In contrast, more recent data from out lab indicate that rats that exercise during adolescence (4-6 weeks old) show the opposite pattern: faster learning of the set-shift (Set 2) but not the initial discrimination (Set 1). Because the set-shift is mediated by the prefrontal cortex, our data support the idea that the adolescent rodent prefrontal cortex is more amenable to the effects of exercise than the adult prefrontal cortex. We are currently pursuing the generality of this idea by examining the effects of exercise on a second prefrontal-dependent phenomenon: renewal of extinguished instrumental lever-pressing. Data will be presented showing that voluntary exercise during adolescence reduces instrumental forms of renewal and that instrumental renewal is mediated by the medial prefrontal cortex. Supported by NIH/NIMH R01 MH082893.

The role of behavioral flexibility in anxiety vulnerability. Jennifer E. Catuzzi Fragale 1,2, Kevin D. Beck1,2, and Kevin C.H. Pang1,2. 1Neurobehavioral Research Laboratory, Research Service, VA New Jersey Heath Care System, East Orange, NJ 07018, USA**.** 2Graduate School of Biomedical Sciences, New Jersey Medical School, Rutgers, The State University of New Jersey, Newark, NJ 07103, USA Behavioral flexibility refers to one's capacity to adapt learned behaviors to accommodate unexpected changes in the environment. Flexible learning is dependent on activation of the ventromedial prefrontal cortex (vmPFC) and several neuropsychiatric disorders associated with vmPFC dysfunction exhibit a lack of behavioral flexibility. Anxiety disorders are among the group of neuropsychiatric disorders associated with vmPFC dysfunction and inflexible behaviors. One of the most striking examples of inflexible learning in anxiety disorders is the presence of pathological avoidance. However, studies investigating the role of behavioral flexibility in anxiety disorders have provided inconsistent findings. In the present study, we sought to determine if inflexible rule learning represents an anxiety vulnerability factor. Using a model of anxiety vulnerability, the Wistar Kyoto (WKY) Rat, we sought to address this question. WKY rats naturally exhibit inflexible learning in the form of extinction resistant avoidance and exhibit an innate lack of NMDA-dependent long-term potentiation in a sub-region of the vmPFC. Thus, we hypothesized that anxiety vulnerable WKY rats would naturally lack behavioral flexibility. Anxiety vulnerable WKY and non-vulnerable Sprague Dawley (SD) rats were tested in a maze-based set shifting task. In this task rats were presented with two stimulus domains (color and texture) with only one domain predictive of reinforcement. Once the initial rule was acquired the reinforced domain was switched to the previously irrelevant domain. Our results show that WKY rats acquired initial rule learning faster than SD rats. Surprising, WKY rats also acquired extradimensional shifts faster than SD rats. This result was associated with a significant decreased in perseverative errors by WKY rats. While on the surface it appears that WKY rats show greater behavioral flexibility, these results may actually stem from a lack of proactive interference observed in anxiety vulnerable individuals. These results provide insight into the development of anxiety disorders, as anxiety vulnerable individuals may learn stimulus associations separately and be unable to integrate information to adapt behavior. Funding: The research presented in the current study was funded by the Biomedical Laboratory Research and Department of Veterans Affairs Office of Research & Development (1I01BX000218 and I01BX000132), the NIH (RO1-NS44373).

1:00-3:00 **What do rodent ultrasonic vocalizations reveal about brain function, affective states and communication?** Chair: **Paul B.S. Clarke.**

Ultrasonic vocalization and emotional arousal systems. Stefan M. Brudzynski, Department of Psychology, Brock University, St. Catharines, Ontario, Canada. Rats emit ultrasonic vocalizations in biologically significant situations that are associated with emotional arousal. Vocal communication of emotional states evolved as a highly adaptive social tool. Rats emit 50 kHz calls in positive, appetitive and rewarding situations, or 22 kHz calls in negative, aversive and dangerous situations. These two classes of ultrasonic calls are signaling to conspecifics appetitive or aversive state that is initiated in the brain by one of two independent tegmental ascending systems: the mesolimbic dopaminergic system for positive arousal and the mesolimbic cholinergic system for negative arousal. Recent functional maps of these systems, particularly the mesolimbic dopaminergic system provided new insight into the initiation of emotional arousal. These two ascending emotional arousal systems function in an antagonistic way to each other and work largely in a mutually exclusive way, as it was documented by recent pharmacological results. Emission of ultrasonic vocalizations appeared to faithfully and quantitatively reflect emotional arousal and the valence of emotional state in the rats. Results of these studies provide insight into early evolution of basic emotive system and mechanisms of emotional arousal in the mammalian brain. Supported by Natural Sciences and Engineering Research Council of Canada.

Neurobiological factors involved in production and perception of pro-social 50-kHz ultrasonic vocalizations in rats. Wöhr, Markus1; PhD. 1 Behavioral Neuroscience, Philipps-University, Marburg, Germany. Rats emit distinct types of ultrasonic vocalizations (USV), which serve as situation-dependent affective signals with important communicative functions. Low-frequency 22-kHz USV typically occur in aversive situations, such as social defeat or predator exposure, whereas high-frequency 50-kHz USV can be observed in appetitive situations, like social play in juveniles or mating in adults. Importantly, the two main USV types serve distinct communicative functions and induce call-specific behavioral responses in the receiver. While 22-kHz USV probably serve as alarm calls and induce freezing behavior in the receiver, 50-kHz USV lead to social approach behavior, indicating a pro-social, affiliative communicative function. The opposite behavioral responses are paralleled by distinct patterns of brain activation. Freezing elicited by alarming 22-kHz USV is accompanied by increased neuronal activity in brain areas regulating fear and anxiety, such as the amygdala. In contrast, social approach behavior evoked by pro-social 50-kHz USV is paralleled by reduced activity levels in the amygdala, but enhanced activity and dopamine release in the nucleus accumbens, a brain area implicated in reward processing. Importantly, the emission of pro-social 50-kHz USV by the sender but also the behavioral response elicited in the receiver can be modulated by manipulating major neurotransmitter systems, including dopamine and serotonin, but also other systems strongly implicated in regulating social behavior, such as opioids and vasopressin. Together, this indicates that affective USV might be an important tool for studying the neurobiology underlying socio-affective communication, which is particularly relevant for rodent models of neuropsychiatric disorders characterized by social and communication deficits, such as autism and schizophrenia. (This work was supported by the German Research Foundation.)

Adult rat 50-kHz ultrasonic vocalizations as potential indicators of emotional state. Paul Clarke, McGill University. Adult laboratory rats possess a rich repertoire of ultrasonic vocalizations (USVs), comprising 22-kHz "alarm" calls and an acoustically diverse family of 50-kHz calls which includes at least a dozen call subtypes. The acoustic complexity of 50-kHz USVs offers a rich source of information which may lend itself to the development of novel animal models. Some 50-kHz vocalizations (e.g. "flat" and "trill" calls) are prevalent in a wide variety of behavioral contexts; other call subtypes are usually less common. The proportional contributions of each call subtype collectively define the call profile. A number of manipulations, both behavioral and pharmacological, alter the call profile independently of any effect on call rate. The effects of drugs on 50-kHz calling appear distinct from their effects on other measures such as locomotor activity, conditioned place preference, and drug discrimination. Although 50-kHz USV emission is strongly dopamine-dependent, 50-kHz calls were not consistently evoked by optogenetic stimulation of ascending dopaminergic neurons, using optical parameters that were highly reinforcing. The functional significance of individual 50-kHz call subtypes remains largely unknown, although frequency-modulated calls are widely believed to represent a positive emotional state. The trill call subtype, in particular, is especially prominent during rat play, and after administration of amphetamine,

cocaine and morphine; for these and other reasons, trill calls have been proposed as a marker of positive affect. This proposal will be critically discussed. Supported by NSERC and CIHR (Canada).

Ultrasonic vocalizations as motivational and emotional markers during social interactions in mice. Granon, Sylvie1; Cressant, Arnaud1,2; Chauveau, Frédéric3; Pittaras, Elsa1,3; Faure, Alexis1 1. CNRS 9197, Paris Sud University, Paris Saclay Institute for Neuroscience, France 2. now at Brain@vior, France 3. Institut de Recherche Biomédicale des Armées, Brétigny sur Orge, France. Our work aims at understanding which factors influence ultrasonic vocalizations (USVs) in male mice during social interactions in order to grasp their putative significance. We have recorded USVs emitted between adult male mice engaged in different kinds of social interactions (free in novel a cage, three-chamber, one mouse anesthetized...) and after various rearing experience (social isolation, grouped, enriched environment). In addition, we will show important mouse strain differences, mostly related to emotional differences. We will thus report the factors that are modulating USV features and repertoire, and will have elements to argue that mouse USVs are strongly influenced by the motivation for social contact, their previous experiences, and their emotional level, making USVs non invasive physiological index of emotion and motivation. The data discussed here will thus have implications for how behavioural experiments are carried out as well as for putative neurobiological support of acoustic communciation during social interaction. Supported by CNRS and University Paris Sud (France).

3:30-5:30 **Inhibition and reward: Are they related?** Chairs: **Harriet de Wit, David Jentsch.**

Stop in the name of DRD2! Linking inhibition and reward through genetics. J. David Jentsch1, 1Department of Psychology; University of California, Los Angeles. Historically, a number of biobehavioral traits have been shown to segregate with substance use disorders, particularly heightened impulsivity and sensitized incentive motivation. Recent data suggest that this phenotypic association may result from the fact that impulsivity and motivational tone are heritable risk factors for substance use disorders, possibly through influencing the initiation of drug-taking behavior, or its escalation with extended experience with the drug. The concept that heritable variation in impulsivity or incentive motivation is a susceptibility factor for the initiation of drug-seeking was tested using an inbred mouse reference panel (the hybrid mouse diversity panel). Phenotypes indicative of impulsivity (reversal learning), incentive motivation (operant responding for a sweet reward) and drug-taking (intravenous cocaine self-administration) were assessed in large numbers of strains (~100, ~75 and ~50, respectively). Analyses showed that all are heritable traits and that impulsivity, but not incentive motivation, is genetically correlated with drug self-administration behaviors. At a molecular level, expression of DRD2 in multiple brain regions also predicted impulsivity, an effect supported by molecular imaging studies in non-human primates. Genome-wide association revealed non-overlapping quantitative trait loci for the three traits. Weighted gene co-expression network analyses of brain gene expression traits identified eigengenes with expression that correlated with the behavioral traits, and transcripts expressed from the linked quantitative trait loci were involved in correlated gene expression modules. These studies underscore the potential of systems genetic approaches to uncover novel biological mechanisms giving rise to the segregation between high impulsivity and elevated drug-taking behaviors.

Reward valuation in withdrawal and abstinence: Roles of striatal D2 and BDNF. Alicia Izquierdo. UCLA, Department of Psychology, Brain Research Institute. Psychostimulant experience produces many neurobiological changes that, in part, result in increased valuation of rewards and/or decreased sensitivity to their costs. Recent data collected in our lab supports the idea that during long-term withdrawal and abstinence from methamphetamine, animals exhibit enhanced sensitivity to positive feedback and exert greater physical effort for larger magnitude food rewards (Stolyarova et al. 2014, 2015). By extension, these alterations may contribute to enhanced reinstatement of drug-seeking behavior when, once again, drug is an available option. Many of these behavioral alterations have been associated with activity at the dopamine D2 receptor in the striatum. Additionally, brain-derived neurotrophic factor (BDNF) and its action at the TrkB receptor is important in LTP in the striatum (Jia et al. 2010). Therefore, TrkB signaling in the striatum may be important in learning about current conditions of reward availability. We quantified

changes in both D2 and phosphorylation of the TrkB receptor (pTrkB) via western blot in the striatum of Long-Evans rats after methamphetamine experience. Tissue was collected either 1 day after methamphetamine experience (escalating doses, culminating at 6.0 mg/kg over 2 weeks) or six weeks after the last dose. We found that expression of both D2 and pTrkB was elevated 1 day after methamphetamine, but returned to baseline after six weeks, indicating that a transient window of plasticity is opened during early withdrawal from methamphetamine. A separate group of rats was treated with the same dosing regimen and subsequently tested on a cognitively effortful 3-way visual discrimination task wherein animals had to nosepoke stimuli to obtain food rewards. Methamphetamine-, but not saline-treated rats, were able to learn the task to an 85% criterion, providing functional evidence of this enhanced plasticity. This supports the idea that conditions in the environment when TrkB signaling is elevated can inflate reward valuation during withdrawal. We propose that the negative state of early withdrawal may undergo enhanced consolidation, and result in increased reward sensitivity in prolonged abstinence. These results are discussed with reference to the extensive literature on reversal learning impairments, and the timing of those observed impairments, after psychostimulant exposure.

I can't stop myself, I like it: Inhibition and drug reward. Harriet de Wit1 and Jessica Weafer1**.** 1 Department of Psychiatry and Behavioral Neuroscience, University of Chicago**.** Two traits thought to predict drug abuse and other excessive behaviors are impulsivity and sensitivity to the rewarding effects of incentive stimuli. Individuals who have difficulty inhibiting inhibit maladaptive behavior are at risk for excessive drug use, as are individuals who experience greater-than-average reward from pleasurable stimuli, including the drugs themselves. Either of these traits could independently increase the risk of engaging in maladaptive behaviors such as drug abuse. Interestingly, recent preclinical evidence suggests that the two traits share common neurobiological mechanisms, and that a single underlying neurobiological risk variable may affect both impulsive behavior and reward. We have examined these associations in healthy young adults, by studying the relationship between behavioral indices of impulsivity and the euphorigenic effects of single doses of drugs, including amphetamine and alcohol. Healthy young adults completed behavioral measures of impulsive behaviors, and on a separate occasion received single doses of methamphetamine or placebo under double blind conditions. Individuals who exhibited poor behavioral inhibition on the Stop Task also reported greater euphoria after a single oral dose of amphetamine.

Right inferior frontal gyrus and the suppression of motor and reward processes. Hugh Garavan, University of Vermont, USA. My talk will focus on the integrity of inhibition processes as a risk factor for adolescent drug use. I will present results from the IMAGEN project (http://www.imagen-europe.com), a longitudinal study of 2,000 European adolescents containing extensive genetic, neuroimaging and phenotypic assessments. The subjects were assessed at age 14, prior to significant drug use, with follow-up data available at ages 16 and 18. The analyses focus on motor response inhibition (the STOP task) as well as impulsive choices (Delayed Discounting). Analyses of the STOP task (n=1,896 fourteen year olds) revealed distinct brain networks associated with different aspects of diminished inhibitory control, dissociating networks linked to drug use from those connected with ADHD symptoms. Hypofunctioning of an orbitofrontal network was associated with increased likelihood of adolescent alcohol use. Right inferior frontal activity was related to inhibition processing speed, illicit substance use, and genetic variation in a norepinephrine transporter gene. More recent analyses have revealed the brain structural correlates of delayed discounting. Here, we show that those who discount future rewards more steeply have reduced grey matter volumes in the ventro-medial prefrontal cortex but increased volumes in the ventral striatum. Moreoever, the ratio between these cortical and subcortical volumes is related to levels of substance use. More specifically, this ratio mediated the relationship between early life adversity and subsequent substance use and externalizing behaviors. Combined, the results suggest that both impulsive responding and impulsive choice are related to adolescent drug use and both may, in part, constitute pre-existing traits that confer vulnerability for use. A number of frontal systems are associated with the risk of use with the evidence implicating ventral PFC as particularly important.

3:30-5:30 **Seeing through the smoke: Human and animal studies of cannabis use and endocannabinoid signalling in corticolimbic networks.** Chairs: **Iain McGregor, Wendy Adams.**

Sterol carrier protein-2 selectively regulates endocannabinoid signalling in the amygdala. Cecilia J. Hillard, Medical College of Wisconsin. Sterol carrier protein 2 (SCP-2) is an intracellular lipid transport protein that transports cholesterol, fatty acids and the endocannabinoids (eCBs). We have shown recently that SCP-2 can facilitate the cellular accumulation of the eCBs. SCP-2 is expressed in the amygdala, and we tested the hypothesis that loss of SCP-2 potentiates CB1 cannabinoid receptor (CB1R) signaling in the amygdala. In support of this hypothesis, SCP-2 knock out mice exhibit enhanced extinction of fear and this enhancement is reversed by CB1R blockade. However, concentrations of the eCBs AEA and 2-AG were not increased in amygdala from the SCP-2 knock out mice; in fact, 2-AG concentrations were significantly reduced. On the other hand, amygdalar CB1R mRNA expression and binding site density were both significantly increased in the SCP-2 knock out mice compared to wild type controls. CB1R expression and binding site density were not increased in other brain regions, including hippocampus, prefrontal cortex and cerebellum. These findings suggest that reduced SCP-2 function results in enhanced CB1R function in the amygdala through an as-yet unknown mechanisms. These data have relevance for discovery of mechanisms by which CB1R function can be selectively enhanced in the CNS. Supported by NIDA grant R01 DA09155 and the Advancing a Healthier Wisconsin Endowment at the Medical College of Wisconsin.

Hippocampal Cannabinoid Transmission Modulates Mesolimbic Neuronal Activity States and Regulates Emotional Processing and Social Cognition: Implications for Schizophrenia. Steve Laviolette, PhD. In schizophrenia, negative symptoms characterized by social withdrawal disturbances and positive symptoms associated with dysregulation of emotional processing, are associated with mesolimbic dopamine (DA) dysfunction. Cannabinoid exposure and/or activation of central CB1 receptors (CB1R) can strongly modulate the mesolimbic system and produce psychotomimetic effects resembling schizophrenia. The mammalian ventral hippocampus (vHIPP) is a critical limbic input to the mesolimbic pathway, controlling DAergic activity via direct and indirect connections with the ventral tegmental area (VTA) and nucleus accumbens (NAc). Importantly, over-activation of the vHIPP is a well-established neuropathological feature of schizophrenia, effects that are hypothesized to be due to loss of inhibitory control over excitatory vHIPP outputs to mesolimbic targets. CB1Rs are highly expressed in the mammalian nervous system, including the hippocampus, where their activation has been reported to reduce tonic inhibitory tone in both humans and rats. However, the functional interplay between vHIPP CB1R transmission and mesolimbic neuronal activity states is not well understood. Using single-unit *in vivo* electrophysiological recordings in the VTA and NAc, we report that intra-vHIPP CB1R activation strongly increases both VTA DAergic and NAc neuronal activity states. Furthermore, using a combination of reward memory assays (morphine conditioned place preference) social cognition and fear conditioning, we report that intra-vHIPP CB1R activation dramatically amplifies the emotional salience of normally sub-threshold reward or aversion-related behavioural conditioning. Furthermore, vHIPP CB1R activation causes profound disturbances in social cognition behaviours. These phenomena were found to be dependent upon DAergic and glutamate receptor (AMPA/NMDA) substrates, directly in the NAc. Collectively, these results provide novel evidence that overstimulation of hippocampal CB1R transmission not only potently controls mesolimbic activity states, but may induce schizophrenia-like behavioural disturbances resembling either positive or negative symptomology.

THC decreases cognitive effort without impairing attentional processes: The role of the cannabinoid system in a distinct form of cost/benefit decision-making. Mason M. Silveira (1), Wendy K. Adams (1), Catharine A. Winstanley (1). (1) Department of Psychology, University of British Columbia, Canada. Cannabis is the most commonly used illicit substance worldwide, with a purported 10% of the Canadian population using the drug in the past year alone. The increasing popularity of cannabis is likely a consequence of growing societal acceptance around its use both recreationally and

medically. However, the drug is linked to a number of adverse cognitive and psychosocial impairments, and longitudinal studies indicate that cannabis use is associated with less educational attainment, less work commitment, and higher rates of welfare dependence. These prospects may reflect a fundamental impairment in effortful cost/benefit decision making, whereby cannabis impairs the willingness to expend the greater cognitive effort associated with advantageous outcomes. To establish a causal role of cannabinoid signaling in such cost/benefit decision-making, we evaluated the effects of various cannabinoid drugs on the rat Cognitive Effort Task (rCET). In this task rats must choose between two options differing in reward magnitude (two pellets versus 4 pellets) but also in the amount of cognitive effort required to obtain these rewards (easy (1s) versus hard (0.2s) visuospatial discriminations, respectively). Thirty-two Long-Evans rats were trained on the task and administered the following drugs: rimonabant, a CB1 receptor antagonist; AM 630, a CB2 receptor antagonist; URB597, a FAAH inhibitor which prevents the breakdown of the endogenous cannabinoid anandamide; Δ-9 tetrahydrocannabinol (THC), the main psychoactive component of cannabis; and cannabidiol, a phytocannabinoid linked to the purported therapeutic effects of cannabis. These drugs affected a variety of behavioural measures, but only THC affected decision making. Specifically, THC decreased cognitive effort at all doses tested, thereby making rats less willing to initiate hard attentional trials associated with larger reward. Importantly, this decrease in effortful choice was observed across rat groups differing in baseline choice performance (termed “workers” and “slackers”), and cannot be attributed to impaired cognitive ability, as THC leaves attentional faculties intact. Data relating the THC effect to CB1 receptor expression levels in prefrontal and limbic structures will also be presented. This investigation is the first of its kind to implicate the cannabinoid system in effortful cost/benefit decision-making, and suggests that impaired decision-making processes may underlie the adverse psychosocial outcomes associated with cannabis use.

6:00 **Early Career Award.** Introduction: **Stephen Kent**

Unraveling frontal lobe dysfunction after traumatic brain injury using preclinical models. Corina Bondi1-3, Megan LaPorte1,2, Heather, Tennant1,2, Kristin Free1,2, Jeffrey Cheng1,2, Anthony Kline1-6. 1Physical Medicine and Rehabilitation, 2Safar Center for Resuscitation Research, 3Center for Neuroscience, 4Psychology, 5Critical Care Medicine, and 6Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, Pennsylvania. Traumatic brain injury (TBI) models in the laboratory have been associated for decades with declines in long-term learning and memory, although the types of behavioral tests performed to date did not focus on the complex attention impairments related to the frontal lobe, which are common in most brain injuries. Specifically, executive function and cognitive flexibility represent sophisticated brain capabilities to use environmental feedback to “unlearn” a previously valid set of rules, switch gears and filter out unwanted distractions. We have begun to employ the attentional set-shifting test (AST), a complex cognitive paradigm analogous to the Wisconsin Card Sorting Test, which is used to measure strategy-switching deficits in patients with frontal lobe damage, TBI, and psychiatric disorders. Previously, we demonstrated that a controlled cortical impact (CCI) injury produced significant impairments in executive function and cognitive flexibility in the AST. In the current study, clinically relevant therapies for cognitive performance deficits after traumatic brain injury were used alone and in combination. Specifically, the enriched environment (EE) housing strategy is an endorsed animal model of rehabilitation, while daily injections of the antidepressant drug citalopram, a treatment known to alleviate depressive-like symptoms and improve cognition in humans, were also provided alone or in combination with EE. The combined treatment aims to mimic simultaneous rehabilitation and pharmacological treatments given to patients in a clinical setting. EE exposure provided significant cognitive recovery when tested four weeks post-injury, although performance may further benefit from combined therapy with citalopram, as preliminary findings indicate. Future studies will continue to investigate in more detail the ideal cognitive recovery timeline and specific brain pathways and mechanisms involved in restoring higher function after TBI. Supported, in part, by NIH grants HD069620, NS060005 and NS084967 (AEK).

6:30-8:30 Oral Session 1. Chair: **Matthew Hale**

Systemic modulation of dopamine D2/D3 receptors revert orbitofrontal neurophysiological neural correlates of risk preference in a rodent gambling task of decision-making under uncertainty. Vasco Galhardo1,2, Helder Cardoso-Cruz1,2, Clara Monteiro1,2, Margarida Dourado1,2. 1. Departamento de Biologia Experimental, Faculdade de Medicina, Universidade do Porto, 4200-319 Porto, Portugal. 2. Instituto de Biologia Molecular e Celular - IBMC, Universidade do Porto, 4150-180 Porto, Portugal. Dopaminergic signaling in orbitofrontal cortex (OFC) is thought to be critical for sustaining the neural representations of events critical for risk assessment during decision-making processes. It has been recently described that chronic pain patients and animal models of pain present disrupted risk assessment in emotion-based decision tasks under ambiguity such as the Iowa Gambling Task or the Rodent Gambling Task (RGT). Moreover it has also been shown that severe stressful conditions such as chronic pain, cause morphological and neurophysiological changes in prefrontal areas. However, it remains unclear whether pain-related changes in local OFC networks depend on dopaminergic modulation. In this study, we investigated whether the pharmacological modulation of D2r receptors activity alters pain-related abnormal risk-assessment and OFC neural representation during performance in the RGT probe session of decision-making under ambiguity. Briefly, the RGT is a two-lever free choice task in which naïve animals are exposed to new and uncertain reward probabilities associated with the two levers: over 90 trials the animals explore the contingencies and express a preference for either the low risk (1 food pellet at 0.9 chance) or the high risk lever (3 food pellets, 0.3 chance). Our previous studies have shown that control animals prefer the low-risk lever, while OFC-lesioned or animal models of pain prefer the high risk lever. To study the effect of dopamine modulation in the neurophysiological correlates of RGT performance, we implanted intracranial matrices of 8 tungsten electrodes in awake freely moving rats, and recorded the neural activity of populations of neurons in the OFC during performance in the RGT. Recordings were performed during the RGT training phase and during the testing probe sessions of risk assessment, and were repeated before and after the induction of the CFA model of inflammatory pain. We compared the behavioral performance and neurophysiological activity profile after the systemic or intra-OFC administration of either saline, D2/D3r agonist quinpirole (0.05 mg/ml) or D2/D3 antagonist raclopride (0.05 mg/ml). Our results show that both drugs disrupt normal performance in control animals, but systemic raclopride restores preference for the low risk lever in CFA animals. Intra-OFC administration was only able to partially reverse the impaired performance. The cluster analysis of OFC neural correlates shows that raclopride restores single lever specifity. Supported by FCT Grants SFRH/BD/70522/2010, SFRH/BPD/92203/2013 and PTDC/NEU-SCC/1516/2012.

Chronic stress and ablation of neurogenesis independently reduce hippocampal volume. Timothy Schoenfeld1, Hayley McCauseland1, Heather Cameron1. 1Unit on Neuroplasticity, National Institute of Mental Health. Despite the majority of research linking the hippocampus (HIP) to learning and memory, HIP volume loss has been suggested as a hallmark symptom of major depressive disorder. MRI studies indicate that HIP volume is decreased in patients with major depression and normalized by antidepressant treatment. Similar changes associated with adverse life events and glucocorticoid treatment suggest that stress may be involved in this volume decrease. In animal models, chronic stress produces dendritic atrophy in CA3 pyramidal cells and inhibits the ongoing production of dentate gyrus (DG) granule neurons. It is not known whether these cellular-level changes associated with depression can decrease the overall size of the HIP or how the effects in the two regions are related. We therefore measured HIP volume in rats following inhibition of neurogenesis, chronic stress, or a combination of both. We treated GFAP-TK transgenic rats with valganciclovir beginning at 8 weeks of age to specifically inhibit adult neurogenesis. We chronically stressed some rats using daily restraint, changing the timing, duration, and context of stress to prevent habituation to the stressor. Volume was measured using both MRI of whole brains with a 14.1T scanner and computer-assisted histological tracing in brain sections. Stressed rats but not rats with ablated neurogenesis showed a depressive phenotype in the novelty-suppressed feeding test. After 4 weeks of stress, wild type (WT) rats showed dendritic loss in granule cells and CA3 pyramidal cells and overall volume loss throughout the HIP. After 4 weeks of inhibiting neurogenesis, GFAP-TK rats showed atrophy of CA3 pyramidal cells but not granule cells, and significant loss in DG volume, but no significant overall HIP volume loss compared to WTs. Volume loss beyond the

DG was not seen in GFAP-TK rats until at least 8 weeks of ablated neurogenesis. In GFAP-TK rats, 4 weeks of stress did not further induce atrophy in neurons nor decrease HIP volume, but did decrease CA1 volume, as in stressed WTs. These data show that specific inhibition of adult neurogenesis and chronic stress both produce cellular and volumetric changes in the HIP. However, the different effects on behavior, different time courses and different subregions affected by these two manipulations suggest that some but not all of the effects of stress on HIP structure and depressive-like behavior are produced by inhibition of adult neurogenesis.

Neurochemical and behavioral comparison of contingent and non-contingent methamphetamine exposure using binge and long-access yoked self-administration paradigms. Keck, Thomas M.;1,2, Schweppe, Catherine;1 Burzynski, Caitlin;1 Ladenheim, Bruce;1 Cadet, Jean Lud;1 Gardner, Eliot L.;1 Xi, Zheng-Xiong Xi;1 van Praag, Henriette;3 Newman, Amy H.1. 1NIDA-IRP, NIH, Baltimore, MD USA; 2Rowan University, Glassboro, NJ USA; 3NIA-IRP, NIH, Baltimore, MD USA. Abuse of the highly addictive psychostimulant methamphetamine (METH) can cause long-lasting damage to brain monoaminergic systems. Among the profound physical and mental health problems for individual users, METH abuse is associated with cognitive impairments affecting executive function, working memory, and motor performance. Animal models of METH exposure have been useful in dissecting the molecular effects of the drug on cognitive processes, but most studies to date have utilized acute, non-contingent administrations of METH which do not adequately approximate human METH use. Recent reports suggest long-term, contingent METH exposure via long-access (6-hr; LgA) self-administration paradigms may induce cognitive deficits. In this study, we sought to directly compare the differences in behavioral and neurochemical outcomes of rats following non-contingent “binge” METH administration with rats that received chronic METH via contingent or yoked (non-contingent) LgA METH self-administration in order to better understand the role of contingency and patterns of exposure in METH-induced cognitive impairments. Compared to saline controls, METH reduced striatal dopamine and hippocampal 5-HT levels in binge animals but not LgA animals. Hippocampal BDNF levels were reduced in both binge animals and LgA animals; however, hippocampal TrkB levels were increased only in binge animals. No clear deficits were seen in Y-maze or novel object recognition experiments, but contingent LgA animals had decreased performance in a Morris water maze task of spatial learning and memory. These results show that the pattern of drug exposure and the contingency of administration can differentially affect neurochemical outcomes and behavior in cognitive tasks. Research was supported by the National Institute on Drug Abuse-Intramural Research Program, National Institutes of Health

Exploration of the role of GTF2i in the social phenotypes of Williams Beuren Syndrome and Autism Spectrum Disorder. Loren A. Martin1, Erica Iceberg1, Megan Rahman1, Breanna Lum1, Amy Patterson1. Azusa Pacific University. Williams Beuren Syndrome (WBS) is a developmental disorder caused by a deletion of human chromosome 7q11.23 that contains 26 genes. Symptoms of WBS include mild to moderate intellectual disability and hypersocial behavior. Autism Spectrum Disorder (ASD) is a behaviorally-defined collection of syndromes of known and unknown etiology that share a common phenotype including impairments in social motivation. The hypersocial behavior associated with WBS appears opposite to the hyposociality observed in ASD, and interestingly, duplications of 7q11.23 have been associated with ASD. The social phenotype of WBS has recently been linked to the deletion of a single gene: GTF2i, or general transcription factor IIi (TFII-I). Duplication of GTF2i has also recently been associated with ASD, suggesting that it works in a dosage-type response in its effects on social behavior. In this study, we characterized the specific aspects of social behavior that are modulated by GTF2i. Specifically, we compared mice having either a deletion (Gtf2i+/-) or duplication (Gtf2i+/Dup) of Gtf2i to wildtype (WT) littermate controls on a series of social behavior tasks. In the social choice task, Gtf2i+/- mice showed a significant preference for a stimulus mouse that was not observed in WT siblings. During a social encounter, Gtf2i+/- mice spent significantly more time in nose-to-nose contact compared to WT siblings. To assess social motivation, test mice were trained to press a lever for a social reward in the form of 15s access to an unfamiliar stimulus mouse. The number of lever presses achieved in the final trial of a testing session was used as an index of social motivation. Gtf2i+/- mice demonstrated significantly higher numbers of lever presses than WT mice. Results from tests comparing Gtf2i+/Dup mice to WT sibling controls are currently underway and will be presented as well. Overall, results from the

tests on the Gtf2i deletion mice support a role for this gene in the hypersocial phenotype of WBS. Opposite results from Gtf2i duplication mice will support a role for this gene in the hyposocial phenotype of ASD and help establish GTF2i as a modulator of social behavior.

The role of endogenous dynorphin in depression-like behaviors in C57/BL6 mice. Lutfy, Kabirullah1; Hamid, Abdul1; Marquez1, Paul1; Chan, Patrick2. 1Pharmaceutical Sciences Department; 2Department of Pharmacy Practice and Administrative Department, College of Pharmacy, Western University of Health Sciences, Pomona, California, USA. Recent evidence suggests that the endogenous dynorphin/kappa opioid receptor system is involved in depression-like behaviors. This system has also been implicated in depression-like behaviors that develop following drug withdrawal. However, whether there is a gender related difference in these processes is unknown. Thus, using male and female mice lacking the prepro-dynorphin gene and their wild-type littermates/controls, we sought to determine the role of endogenous dynorphin in depression-like behaviors using the forced swim test, which is widely used as a model of depression in rodents. We also assess if depressive-like behaviors would be different between mice of the two genotypes 8 days following a single amphetamine compared to saline injection. We also determined if the motor stimulatory action of amphetamine would be different between mice of the two genotypes and if there is any gender-related difference in this response. To this end, male and female mice lacking the prepro-dynorphin gene and their wild-type littermates/controls were brought to the laboratory and allowed to habituate to the testing room for 1 h. Mice were then placed in a beaker ¾ filled with water (temperature = 23□C) and forced to swim for 15 min. The next day, mice were brought to the testing room, habituated for 1 h and then tested for immobility time. On this day, each mouse was placed in the water and allowed to swim for 15 min. The amount of time that mice spent swimming and remained immobile was recorded and used for data analysis. For motor activity measurement, mice were brought to the laboratory and habituated to the testing room for 1 h. Mice were then injected with saline or amphetamine (3 mg/kg) and the distance traveled during the 1-h test period was recorded for each mouse. A week later, mice were also tested for immobility time, as described above. Our results revealed that no significant different was observed between mice of the two genotypes in immobility time. However, female wild-type mice remained immobile for a longer time compared to male wild-type mice and this difference was absent between male and female mice lacking dynorphin. Interestingly, female wild-type mice were also found to be more sensitive to the motor stimulatory action of amphetamine compared to their respective male mice. However, endogenous dynorphin was not involved in this process because female of either genotype showed a greater sensitivity to the action of amphetamine. On the other hand, there was an interaction between gender and endogenous dynorphin, i.e., male mice lacking dynorphins showed a reduced response to the amphetamine challenge compared to their wild-type littermates/controls. Nevertheless, no difference was observed in depression-like behaviors 7 days following withdrawal from acute amphetamine in mice of either genotype. Together, these results suggest that endogenous dynorphin/kappa opioid receptor system may be involved in gender-related difference in depression-like behaviors but not in the action of acute amphetamine or withdrawal from acute amphetamine.

Pharmacological assessment of a role for orbitofrontal adrenoreceptors in yohimbine-induced enhancement of motor impulsivity. Wendy K Adams1,2, Fiona D Zeeb1, Paul J Cocker1, Michael M Barrus1, James Benoit1, Catharine A Winstanley1,2. 1Department of Psychology, University of British Columbia, Vancouver, BC, Canada; 2UBC Institute of Mental Health, University of British Columbia, Vancouver, BC, Canada. The α2 adrenoreceptor antagonist, yohimbine, is used as a pharmacological tool to model aspects of the stress response, with increased noradrenaline release following blockade of central, inhibitory autoreceptors thought to underlie its anxiogenic effects. For example, yohimbine administration can increase impulsivity in healthy subjects and induce psychiatric symptoms, such as mania and panic attacks, in vulnerable individuals. We previously reported that yohimbine treatment increases motor impulsivity in rats performing the 5-choice serial reaction time test (5CSRTT), in a manner dependent on the activation of cAMP response element binding protein (CREB) in the orbitofrontal cortex (OFC). Therefore, the present study set out to investigate the putative contribution of post-synaptic α1-, α2- and β-adrenoreceptors in the OFC on yohimbine-induced alterations in 5CSRTT performance. Male Long-Evans rats were trained in the 5CSRTT before being surgically implanted with guide cannulae into the OFC. The α1-adrenoreceptor antagonist, prazosin, and β-adrenoreceptor antagonist, propranolol, were administered either into the OFC or systemically prior to systemic

yohimbine treatment and 5CSRTT performance was assessed. The behavioural effects of intra-OFC administration of yohimbine itself were also assessed. Blockade of α1- or β-adrenoreceptors in the OFC had no effect on 5CSRTT performance with or without systemic yohimbine treatment. However, systemic administration of α1- or β-adrenoreceptor antagonists attenuated the yohimbine-induced enhancement of impulsivity. In contrast to its systemic effects, local infusion of yohimbine into the OFC was also found to reduce impulsivity. Taken together, these data indicate that the effects of local blockade of α1-, α2- or β-adrenoreceptors in the OFC are dissociated from the effects of systemic treatment. Yohimbine-induced impulsivity due to enhanced CREB signalling in the OFC does not appear to involve the activation of local, post-synaptic adrenoreceptors.

Limbic neuropeptide y-1 receptors modulate vulnerability to social and metabolic challenges depending upon gender and maternal care. Palanza P.1 , Paterlini S1, Panelli R1, Gioiosa L1, Parmigiani S1, Mele P2, Longo A2, Eva C2. 1Dept. of Neuroscience, University of Parma, Parma, Italy; 2NICO, Neurosci. Inst. of the Cavalieri Ottolenghi Fndn, Univ. of Torino, Torino, Italy. Interaction between genes, sex, early developmental events and stress plays a crucial role in the development of psychological and metabolic disorders. Neuropeptide Y (NPY) and its receptors have been shown to be involved in individual vulnerability to stress, anxiety, depression and metabolic disorders. We have demonstrated that conditional knockout Npy1r/rfb mice, in which the inactivation of the Npy1r gene was restricted to excitatory neurons of the forebrain in juvenile and adult mice, showed lower body weight growth, increased anxiety and CRH-IR in the PVN in relation to sex and the maternal cares received during the first postnatal week (Bertocchi et al. 2011). We examined social behavior, body weight growth in response to hyperchaloric diet and respone to social stress in mutant and control mice. To remove Dox-induced inhibition of gene inactivation, after birth (PND0), Npy1r/rfb and their control littermates (Npy1r/2lox) were fostered to lactating mice displaying high (HM- FVB/J and CD1 strain) or low (LM - C57BL/6J) maternal care. During postnatal development, between PND 45 and 100, after conditional Cre-mediated inactivation of the limbic Npy1r gene is induced, Npy1r/rfb male, but not female, mice showed a slower body weight growth compared to controls. Mice were then exposed to either standard diet (STD) or high fat diet (HFD) for 3 weeks. Starting from the second day of HFD, conditional mutant males that were reared by HM foster dams showed a rapid body weight increase that persisted throughout the HFD regimen; no differences were observed in females. While the overall amount of food consumed did not differ from their control littermates, Npy1r/rfb male mice showed higher Kcal intake during the first week of HFD. Npy1r/rfb mutant males exposed to HFD also showed higher levels of the glucose curve in the glucose tolerance test (GTT) and higher perigonadic white adipose tissue as compared to controls and STD mice. These effects were enhanced when male conditional mutants and their control littermates were fed with HFD after been exposed to a chronic psychosocial stress procedure. These results indicate that low limbic NPY1R expression induced by conditional gene inactivation increases susceptibility to hyperchaloric diet and stress in adulthood, and can mediate vulnerability to metabolic disorders in a sex-dependent manner. Also, the early maternal environment affect NPY1R expression in the limbic system, as few or no effects of gene inactivaction were observed in mice reared by LM foster mothers. Support: PRIN2008 PLKP3E_002; PRIN 2010 7MSMA4_005.

6:30-8:15 Oral Session 2: Chair: **Cliff Summers**

The effect of embryonic alcohol exposure on social behaviour and underlying biological mechanisms in zebrafish. Samantha Mahabir1, Diptendu Chatterjee2, Robert Gerlai1,2. 1Department of Cell and Systems Biology, University of Toronto, Toronto, ON. 2Department of Psychology, University of Toronto Mississauga, Mississauga, ON. Fetal alcohol spectrum disorder (FASD) results from the fetus being exposed to alcohol during pregnancy. Individuals that are affected display a range of abnormalities from severe to mild. The biological mechanisms that underlie these effects are complex and poorly understood. Studies using zebrafish show that exposure of embryos to low levels of alcohol disrupts the dopaminergic and serotonergic systems in the developing fish and also causes significant behavioural alterations that are observable even in the adult fish. One potential biological mechanism that alcohol may be acting on is apoptosis. High doses of alcohol exposure to zebrafish early in development have been demonstrated to disrupt the signaling pathway but the doses employed were clinically less relevant. Here we investigate the effects of low embryonic alcohol exposure on social behaviour (shoaling),

neurochemistry, apoptosis and neuronal cell count in specific brain regions in zebrafish. Zebrafish embryos are exposed to alcohol at 24 hours post-fertilization (hpf) for 2 hours using three external bath concentrations, 0.00%, 0.50% or 1.00% (EtOH vol/vol%). Results will be presented on social behavioural responses of the affected fish as well as the amount of neurotransmitters dopamine, serotonin and their metabolites in their brain as compared to control. In addition we will show that exposure to alcohol during embryonic development results in increase apoptotic cell death. To further confirm this result we will analyze expressions of pro-apoptotic proteins using western blot. We will report whether higher cell death is the result of a higher Bax/Bcl-2 ratio in zebrafish embryos exposed to alcohol. We will also present data on the effects of embryonic alcohol on structural characteristics of the adult brain by counting the number of cells in selected brain areas. Preliminary results show a reduction of the number of cells in the olfactory bulb in fish exposed to alcohol. Reduction in neurons or cell population in the central nervous system may be responsible for neurobehavioural effects associated with FAS in humans. Overall, our research will demonstrate that prenatal alcohol induces a range of functional and anatomical changes in the brain. Specifically, we will show that alcohol induced changes in programmed cell death during development may lead to neuronal loss in adulthood resulting in a change in neurochemistry, all of which may affect shoaling behaviour in the zebrafish. Supported by an NIH/NIAAA grant to RG.

Environmental Enrichment Reverses Transgenerational Programming by Early Trauma. McCreary, J. Keiko1; Erickson, Zachary T.1; Babenko, Alena1; Ilnytskyy, Yaroslav2; Olson, David M.3; Kovalchuk, Igor2; Metz, Gerlinde A.S.1. 1 Department of Neuroscience, University of Lethbridge, Lethbridge, Alberta, Canada. 2 Department of Biological Sciences, University of Lethbridge, Lethbridge, Alberta, Canada. 3 Departments of Obstetrics & Gynecology, Pediatrics and Physiology, University of Alberta, Edmonton, Alberta, Canada. Prenatal stress (PS) has been associated with impaired neurodevelopment and related psychopathologies, including depression, anxiety and schizophrenia. We have previously shown in rats that developmental programming by PS propagates across three generations of the maternal lineage, and increases the risk of adverse offspring health outcomes. The objectives of this study were 1) to investigate if PS across several generations affects behaviour and brain morphology via epigenetic regulation, and 2) to determine if environmental enrichment (EE) serves as an effective intervention for ancestral programming. Dams of the parental F0 generation experienced psychosocial stress from postnatal day 90 until parturition. Their pregnant daughters (F1) and grand-daughters (F2) were either stressed (multigenerational prenatal stress; MPS) or remained unstressed (transgenerational prenatal stress; TPS, with stress limited to F0 dams). A non-stress maternal lineage was used for comparison. To test the influence of EE on stress programming, some of the F3 generation were housed in a complex environment from postnatal days 35-180. In the adult F3 offspring, anxiety-like behaviors and fine motor skills were assessed. Histological analysis and microRNA analysis were also performed. The results showed that MPS and TPS increased anxiety-like behaviours and motor impairments. These changes were associated with altered cortical neuron morphology and microRNA profiles. EE in all groups drastically reduced the response to stress across all groups. MPS and TPS animals raised in an EE showed diminished anxiety-like behaviour and improved motor function. EE also had beneficial effects on the stress response, cortical morphology and microRNA profiles. These findings suggest that ancestral stress alters neuronal morphology and lead to mood disorders, psychopathologies, and motor impairments. Overall, EE reversed the consequences of ancestral stress. Epigenetic modifications via microRNAs could be a primary mechanism of stress transfer and reversal by EE, with implications for the discovery of new therapeutic targets or predictive biomarkers of mental health. Acknowledgements: This work was funded by the AIHS Preterm Birth and Healthy Outcomes Team Interdisciplinary Team Grant #200700595 (GM), Alberta Innovates – Health Solutions (GM), and the Canadian Institutes of Health Research (GM). JM was supported by the National Sciences and Engineering Research Council of Canada CREATE #371155.

Localization of phosphorylated AKT in VTA GABA neurons after social stress exposure: Functional implications for stress-induced amphetamine cross-sensitization in rats. Nikulina EM1,2, Johnston CE2, Hammer RP, Jr.1,2. 1 College of Medicine - Phoenix, University of Arizona, Phoenix, AZ; 2 Neuroscience Program, Arizona State University, Tempe, AZ. Intermittent social defeat

stress causes prolonged upregulation of mu-opioid receptors (MORs) in the ventral tegmental area (VTA) and induces cross-sensitization to psychostimulants in rats. MOR signaling includes activation of phosphoinositide 3-kinase (PI3K), and phosphorylation of a serine/threonine kinase, AKT (pAKT). We hypothesized that social stress induces pAKT downstream of VTA MORs, and that VTA AKT phosphorylation is necessary for the expression of stress-induced amphetamine sensitization. First, we used lentivirus-mediated gene transfer and RNA interference to induce persistent bilateral VTA MOR knockdown. Adult male Sprague-Dawley rats were assigned to either viral GFP or MOR knockdown groups, and were subjected either to intermittent social defeat stress, involving a brief confrontation with an aggressive male rat, four times in ten days, or handling. Ten days after the last episode of stress, during the time when cross-sensitization is known to be present, brains were removed and processed for fluorescent immunohistochemical labeling of both pAKT and either glutamic acid decarboxylase (GAD) 65/67, or tyrosine hydroxylase (TH). In the control group, pAKT was almost evenly distributed between GAD65/67 and TH neurons, social stress significantly increased pAKT co-localization with GAD65/67 (~70%) but not TH (<30%), while knockdown of VTA MORs prevented this effect. Taken together, these data suggest that social stress-induced AKT phosphorylation occurs downstream of VTA MORs, and is primarily limited to GABA neurons. Second, to investigate whether AKT phosphorylation is necessary for the expression of stress-induced amphetamine cross-sensitization, a separate cohort of rats underwent bilateral VTA cannula implantation prior to social stress procedures. Seventeen days after the last episode of stress, a dual pAKT/mTORC inhibitor (NVP-BEZ235, 10 µM in 1.0 µl/side) was infused into the VTA 1 h prior to amphetamine challenge (1.0 mg/kg, i.p.). Local inhibition of VTA pAKT blocked the expression of a sensitized response to amphetamine. These data provide evidence that intermittent social defeat stress increases AKT phosphorylation downstream of MORs in VTA GABA neurons, and suggest that VTA MORs act through pAKT to produce psychostimulant cross-sensitization. These results may have implications for therapeutic intervention in stress-induced behavioral disorders.

Sodium butyrate increases contextual fear expression in sign- but not goal-trackers. Christopher J. Fitzpatrick[1], Marcelo A. Wood[2], and Jonathan D. Morrow[1,3]. [1] Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI 48109, USA; [2] Department of Neurobiology and Behavior, University of California at Irvine, Irvine, CA 92697, USA; [3] Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, USA. Pavlovian conditioned approach behavior has been previously used to identify rats that display enhanced fear expression in response to either cues (sign-trackers; STs) or context (goal-trackers; GTs) following fear conditioning (FC). Levels of histone acetylation in brain regions such as the dorsal hippocampus (dHPC) are critical in consolidating contextual FC and may underlie individual variation in contextual fear expression. Therefore, we hypothesized that low levels of contextual fear expression in STs are a result of decreased acetylation following contextual FC. In Experiment 1, we showed that STs express less contextual fear than GTs following contextual FC, despite equal levels of contextual fear during conditioning. In Experiment 2, we demonstrated that sodium butyrate (200 mg/kg; 10 mL/kg), a histone deacetylase (HDAC) inhibitor, given 1 h prior to contextual FC, enhances contextual fear expression in STs, but not GTs. This is the first demonstration that a HDAC inhibitor given before contextual FC can enhance contextual fear expression in some subjects but not others, and suggests that individual variation in histone acetylation during contextual fear conditioning may underlie individual variation in contextual fear expression. In addition, these results may contribute to a neurobiological explanation of why some individuals but not others develop posttraumatic stress disorder. This work was funded by the University of Michigan Department of Psychiatry (U032826; J.D.M.), the National Institute on Drug Abuse (R01 DA036984; M.A.W.), and the Department of Defense National Defense Science and Engineering Graduate Fellowship (C.J.F.).

Mice smell their neighbors' increased pain. Smith ML, Hostetler CM, Li J, Heinricher MM, Ryabinin AE. Oregon Health & Science University. In humans, pain is influenced by social environment. If similar influences occur in laboratory animals they could obscure detecting pain states in experimental animals compared to their co-housed controls. For example, while alcoholics are known to have increased pain sensitivity, the evidence of increased pain in alcohol-consuming laboratory animals is sparse. We performed experiments addressing the hypotheses that withdrawal from voluntary alcohol consumption in mice leads to mechanical hypersensitivity and that this increased mechanical sensitivity induces similar

pain responses in control (bystander) mice housed in the same room with alcohol-consuming mice. Adult male C57BL/6J mice were given 24 hour access to escalating concentrations of ethanol (3-10%) and water in a standard 2-bottle choice drinking procedure and underwent 24 hour-withdrawal sessions once every week. Following mechanical stimulation via von Frey fibers, mice demonstrated hypersensitivity compared to baseline during the first withdrawal session and reached maximum levels of hypersensitivity starting with the second withdrawal session. Surprisingly, water-consuming control mice housed in the same room as alcohol-withdrawing mice also showed mechanical hypersensitivity following one to two weeks of testing. This pain sensitivity was not observed in repeatedly-tested water-consuming control mice housed in a separate room, suggesting social transfer of pain sensitivity from alcohol-withdrawing mice to water controls. Further experiments showed that hypersensitivity in bystander mice is induced via olfactory cues present in the bedding of hypersensitive mice and is accompanied by increased activity in anterior cingulate and insular cortex, brain areas involved in the “pain matrix”. Experiments using the formalin test confirmed that the mechanical hypersensitivity in these mice is also accompanied by hyperalgesia. Conversely, the increased pain sensitivity in bystander mice was not accompanied by increased levels of corticosterone and was not sensitive to diazepam, suggesting that was is not mediated by a generalized stress response in these animals. This first demonstration of transfer of information on pain between rodents housed in the same room has serious implications for the way control groups are designed and interpreted in behavioral studies.

Cholinergic contributions to prefrontal load and attentional capacity in aging. Brittney Yegla1, Jennifer Francesconi1, Vinay Parikh1. 1Temple University. Funding Acknowledgements: National Institute on Aging; American Federation for Aging Research. Cognitive reserve posits that protective measures such as high educational attainment abate age-related memory and attentional decline by enhancing cognitive capacity via structural and functional brain changes. Neuroimaging studies indicate a shift in functional activity during attention-demanding tasks in elderly from occipital to prefrontal regions, termed posterior to anterior shift in aging (PASA). However, the mechanism underlying PASA is unknown. The current study investigates if the compensatory effects from enhanced prefrontal recruitment, as posited in PASA, arise in aging via cholinergic innervation of the prefrontal cortex during attentionally-engaging conditions. Young and aged rats underwent training on an operant sustained attention task (SAT), which required distinction of signal and non-signal trials. On signal trials, a light was illuminated for 500, 50, or 25ms prior to lever presentation whereas no visual cue was presented in non-signal trials. After reaching criterion (≥70% hits and correct rejections), rats received bilateral infusions of cholinergic immunotoxin 192-IgG saporin into the prefrontal cortex (PFC) to produce partial cholinergic deafferentation. Sham controls received saline infusions. Rats returned to SAT and their behavior was assessed at 4 weeks post-surgery. Following the last behavioral session, brains were processed for immunohistochemistry for cfos protein expression to map neuronal activity patterns. A subset of rats served as non-performing controls. Overall, aged rats showed impaired vigilance compared to young rats (main effect of age: $F=6.71$; $p=0.02$). The partial cholinergic lesion interacted with age to produce performance deficits ($F=4.03$; $p=0.03$). Post hoc analysis revealed that aged lesion rats were impaired on 500ms signal durations in comparison to their sham counterparts. Sham aged rats exhibited greater cfos activity in the PFC than young controls ($p<0.05$), but both control groups displayed similar cfos levels in the posterior parietal cortex, another component of the attention network. Restricted loss of prefrontal cholinergic afferents significantly reduced cfos counts in aged rats than sham ($t=2.72$, $p=0.04$). Non-performing aged rats displayed fewer cfos-positive cells (14±2) than their performing counterparts (68.25±8.52) illustrating performance-associated increases in neuronal activity patterns. These data indicate that partial removal of cholinergic afferents disrupted attentional capacity in aged rats with minimal impact on young animals. Moreover, performing aged rats showed greater neural recruitment which was attenuated by prefrontal cholinergic pruning. Our results support the PASA hypothesis and suggest that forebrain cholinergic circuitry may play a significant role in recruiting additional prefrontal neurons for maintaining attentional capacity in aging.

Cross-modulation of cholinergic and GABAergic signaling at the NMJ and resultant effects on C. elegans mobility. Jacqueline K. Rose, Parker Stafford, Nicole Stankowicz, Amanda Leonti, Katrina Mar, Samuel Moss, Andrew Records-Galbraith. Behavioral Neuroscience Program and Department of Psychology, Western Washington University, Bellingham, WA. Several studies have reported modulation of GABA signaling in response to cholinergic agonists and vice versa. At the Caenorhabditis elegans

neuromuscular junction, GABA and acetylcholine receptors are both found postsynaptically on muscle arms and mobility is thought to be mediated by alternating activation of these receptors making the C. elegans NMJ a site where direct interaction between excitatory and inhibitory signaling is plausible. Previous studies from this lab have reported an increase in GABA receptor mRNA transcripts in adult worms, following exposure to the acetylcholine receptor agonist nicotine at early stages in development. More recently, we have examined how GABA and acetylcholine agonist exposure during adulthood affects both GABA and acetylcholine mediated mobility and receptor expression. With regards to mobility, decreases in the number of swim motions (body bends) have been noted following application of either a GABA agonist (via application of GABA or from exposure to toluene, a GABA agonist), or cholinergic agonist alone; however, co-application results in either a recovery of the mobility deficit or sometimes an increase in behavior. At the level of receptor expression, alterations have been examined in vivo at the level of protein with fluorescence imaging of reporter constructs, and mRNA with quantification of transcripts using qRT-PCR. Data indicate that the GABA agonist toluene indeed affects GABA signaling by upregulating presynaptic release mechanisms; early data suggests a change in nicotinic acetylcholine receptor expression as well. Interestingly, unlike previous data showing an effect of nicotine exposure in development on GABA and nicotinic receptor expression, nicotine exposure in adulthood does not seem to influence expression; additional tests are currently under way to confirm. The mobility data suggests that locomotion may rely on a balance between GABA and cholinergic signaling and that some interactive mechanism may exist between these signaling pathways that facilitates cross-modulation. Funding support from WWU Research and Sponsored Programs Project Development Award.

Lipopolysaccharide-induced inflammation increases the expression, but not extinction, of conditioned fear. Young MB1, Howell LL1,2. 1Emory University, 2Yerkes National Primate Research Center. Mounting evidence from psychiatric research has revealed that the mind and the body are linked more intimately than previously appreciated. Psychological stressors can have profound effects on physiology, and traumatic or chronic physical ailments can engender deep psychological distress. However, appreciation is growing for the effects of more subtle immunological disturbances on psychological well-being and how these effects may contribute to psychiatric disorders. Among the best explored observations in this new field of research is the link between peripheral inflammation and depression, as some depressed populations react positively to anti-inflammatory treatments and higher indexes of psychological well-being are associated with reduced expression of pro-inflammatory genes. Less has been studied about how inflammation contributes to severe emotional trauma. Evidence in patients suffering from post-traumatic stress disorder (PSTD) suggests that inflammation may play a part in either its onset or its resistance to recovery through psychotherapy. To begin to explore the relationship between fear and inflammation, we administered a peripheral inflammatory stimulus (lipopolysaccharides; LPS) and measured its effect on the expression and extinction of conditioned cued fear. Administration of LPS before extinction training did not affect the amount of total fear observed during extinction or 48 hours later, when extinction was tested. However, animals treated with LPS exhibited significantly more fear during the first half of extinction training, suggesting that inflammation may increase fear in certain populations, such as those suffering from PTSD. Subsequent studies sought to characterize the physiological and signaling mechanisms underlying this effect, revealing a novel mechanism though which the expression of fear is modulated. This research funded by NIH/NIGMS K12 GM000680.

Friday, June 5

8:00-10:00 **Research Domain Criteria versus DSM V: How does this debate affect attempts to model corticostriatal dysfunction in animals?** Chair: **F. Scott Hall.**

Reducing dopamine transporter expression in mice recreates a mania-like behavioral profile. Jared W. Young[a,c], Arpi Minassian[a], Morgane Milienne Petiot[b], William Perry[a], and Mark A. Geyera,[c]. [a]Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804. [b]Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands. [c]Research Service, VA San Diego Healthcare System, San Diego, CA. The Diagnostic and Statistical Manual of Mental Disorders (DSM) was originally

developed to provide consensus on nomenclature for the serious mental illnesses people suffered from. This consensus lead to a largely descriptive attempt at diagnosing sufferers. Despite consistent development over the years, these diagnostic criteria remain descriptive. Considering serious mental illnesses arise from brain-based disorders however, NIMH has promoted the Research Domain Criteria (RDoC) movement toward depicting deficits by quantifiable behavioral domains as opposed to descriptive nomenclature. Identifying whether specific abnormalities in neuronal functions are linked to specific behaviors and/or disease states remain to be seen. It is clear that dopaminergic dysregulation is associated with numerous psychiatric disorders including attention deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder (BD), Tourette's syndrome, Parkinson's disease (etc.). Neuronal dopaminergic homeostasis is primarily controlled by the dopamine transporter (DAT). Polymorphisms of the DAT have been linked to these disorders, with suggestions of reduced DAT availability putatively underlying behavioral abnormalities of these disorders. The effects of reduced DAT function on behaviors have been investigated using genetic and pharmacological means in tests with cross-species relevance to those used in clinical disorders. We identified that severe reduction in DAT function (75-90% reduction) reproduces behavioral abnormalities consistent with that of BD mania patients. These behaviors include altered exploratory behavior and risk-taking. Inattention is also seen, but in a manner consistent with BD mania and schizophrenia. Considering that reducing DAT can have multiple downstream effects it is surprising how consistent these challenges recreate behaviors observed primarily one disorder (BD mania). Despite lack of group consistency however, we have observed that some patients with a different diagnosis (e.g., schizophrenia) exhibit behavioral abnormalities more consistent with that of BD mania and reduced DAT functioning. Future studies identifying in humans with consistent DAT polymorphisms and measured DAT levels combined with behavioral assessment would be greatly beneficial to understanding similarity of findings.

Dopamine transporter knockout mice as an animal model of attention deficit hyperactivity disorder. Hall, F.S.1. 1Department of Pharmacology and Experimental Therapeutics, College of Pharmacy and Pharmaceutical Sciences, University of Toledo, Toledo, OH, USA. Frontostriatal dysfunction occurs in a number of psychiatric disorders, including ADHD, schizophrenia, mania and addiction. One of the more important issues in current efforts to understand these disorders is the extent to which these disorders involve common underlying causes and mechanisms. Into this discussion has entered the debate concerning the nosology of mental disorders: whether DSM V or RDoC definitions better represent mental disorders. Part of the argument in favor of the RDoC model is that these, and other, psychiatric disorders involve an overlapping group of behavioral phenotypes, in this case differences in impulsivity, attention and executive function, among other symptoms. Over the last decade, behavioral and physiological phenotypes have been characterized in dopamine transporter knockout (DAT KO) mice that are reminiscent of aspects of ADHD. These mice have been described as “hyperdopaminergic” based upon profoundly elevated extracellular levels of dopamine in the striatum. However, as this is not observed in the prefrontal cortex, the physiology of these mice might be better described as resulting in an imbalance in frontostriatal dopamine function. The consequence of this change appears to be a reduction in the activity of frontostriatal projections. These physiological changes are associated with pronounced hyperactivity and highly repetitive locomotor behavior, impairments of sensorimotor gating and impaired risk assessment. Importantly, each of these behavioral deficits is ameliorated by drugs that treat ADHD, including stimulant medications (methylphenidate and d-amphetamine), non-stimulant medications (NET blockers), and even nicotine. In the present context, it is important to note that stimulant drugs that treat ADHD produce the opposite effects in wild-type mice, impairments rather than improvements. Moreover, comparisons to other frontostriatal disorders are quite informative, as stimulants exacerbate, rather than improve, schizophrenic symptomatology. This talk will consider the nature of the DAT KO model in detail, and consider whether this model is more valid as a specific model of ADHD or as a general model of symptomatology independent of specific diagnostic categories.

Chronic dopamine agonist treatment: an animal model of vulnerability to pathological gambling? Winstanley CA**.** University of British Columbia**.** A clinically significant gambling disorder (GD) is

characterized by persistent, maladaptive gambling behavior which disrupts personal and professional life. Improved understanding of the neural and neurochemical basis of gambling could provide valuable insight into GD and stimulate the design of effective treatments. Animal models of gambling behavior could make a significant contribution in this regard. Given the diversity of gambling paradigms, from complex strategy-based card games such as poker, to paradigms with lower cognitive demand like scratch cards and slot machines, one behavioural model is unable to capture all the relevant cognitive processes involved. To this end, we have developed a number of rat behavioral paradigms, based on laboratory tests used clinically to study gambling and gambling-related cognitions, and have demonstrated that the decisions rats make under uncertainty are hallmarked by similar preferences and biases as observed in human choice. It is now well-established that chronic administration of dopamine agonist therapies (DATs) in Parkinson's disease can induce GD, among other addiction and impulse control disorders, de novo in a subset of patients. We have therefore determined the effects of chronic ropinirole treatment on performance of three of our rodent gambling paradigms. In the rat slot machine task (rSMT), chronic ropinirole significantly increased the number of trials completed, indicative of an increased motivation to play the game, without improving or impairing animals' ability to predict reward availability on win vs loss trials. On the rat betting task (rBT), in which rats chose between responding for a certain reward or double that reward or nothing with 50:50 odds, animals showed a marked increase in preference for the uncertain outcome across all bet sizes. In contrast, ropinirole did not alter choice patterns on the rGT, a paradigm based on the Iowa Gambling Task, in which rats must discriminate between four options, each associated with different magnitudes and probabilities of reward and punishment. Comparison of these distinct outcomes suggests that chronic DAT does not impair subjects' ability to determine the most profitable probabilistic options, particularly when losses are explicitly signalled, but may amplify some aspects of the hedonic or incentive value of experiencing uncertainty. The degree to which this may represent an animal model of GD will be discussed.

Modelling corticostriatal dysfunction in schizophrenia. Anne Marie Brady. Department of Psychology and Neuroscience Program, St. Mary's College of Maryland, St. Mary's City, Maryland, USA. Obvious challenges to developing a viable animal model of schizophrenia include the presence of subjective, higher-order clinical symptoms such as hallucinations, delusions, and disordered thought and language. However, patients with schizophrenia also exhibit a range of more fundamental impairments that are amenable to assessment in animal models. The neonatal ventral hippocampal lesion (NVHL) rat model of schizophrenia produces multiple behavioral and cognitive disturbances in adult rats, and these abnormalities are consistent with psychopathology in schizophrenia. This model consists of an early developmental manipulation (an excitotoxic lesion), the effects of which are temporally delayed and appear to arise primarily from disruptions in neural targets downstream from the site of the initial lesion. In particular, the NVHL manipulation produces impairments in multiple domains of cognition which are most closely associated with abnormalities in prefrontal cortical areas and their ventral striatal targets. Morphological and physiological disruptions in prefrontal neurons in the NVHL brain support these behavioral results. Furthermore, the NVHL model can be used to investigate dual diagnosis, the co-morbidity of schizophrenia with substance abuse. The overlaps in behavioral deficits implicated in these two conditions supports recent hypotheses that schizophrenia and addictive behavior may share a common neuropathology. Finally, the broad range of behavioral and cognitive impairments observed in the NVHL model makes it a useful tool to investigate potential treatments and developmental interventions. Supported by NIDA Award DA14020 and Sigma Xi.

8:00-10:00 **Impact of adolescent social experiences on behavior and neural circuits relevant to mental illnesses.** Chair: **Jodi Lukkes, Andrew Burke.**

The role of the cortex in the evolution of social play. Sergio Pellis, Department of Neuroscience, University of Lethbridge. The capacity to engage in rough-and-tumble play is made possible by subcortical neural systems. That is, the cortex is not needed for the play typical of the juvenile period. However, many of the benefits to the development of emotional regulation as well as to social and

cognitive skills depends on the influence of such playful experience on several prefrontal cortical (PFC) systems. Most critically, these play-induced changes produce animals that are more resilient in the face of social and non-social stressors. As such, this would suggest that they would be less prone to depression and anxiety. To achieve this functional influence on the cortex, ancestral patterns of play were modified in ways to maximize the experiences important to produce these effects, but also the cells of the PFC have become sensitive to these experiences. Rats provide a model for exploring these evolutionary changes and the neurobehavioral mechanisms that make these changes possible.

Social defeat during adolescence escalates adult cocaine self-administration: Role of adolescent social experience and adaptive coping behaviors. Andrew R. Burke and Klaus A. Miczek**,** Department of Psychology, Tufts University, Medford, MA, USA. Adverse experiences during adolescence increase the initiation of illicit drug use and the development of addiction. A history of brief intermittent confrontations with a highly aggressive conspecific (i.e. social defeat) promotes greater voluntary self-administration of cocaine in adult rodents, but has not been investigated after social defeat during adolescence. Social housing conditions during adult social defeat alleviate some negative behavioral and physiological outcomes, but the impact on drug self administration is unknown. Thus, we manipulated social experience (housing conditions) and stress history during adolescence and measured cocaine taking in adulthood. Adult residents are less aggressive toward adolescent rodents and the role of housing conditions on adolescent social defeat behaviors have not been studied. We also investigated the effect of age and housing on resident and intruder behavior during the first and last episode of defeat. Rats were housed in pairs (PH) or singly (SH) on postnatal day (P) 21 and then exposed to social defeat or control treatment from P35-44. We assessed novelty- and cocaine-stimulated locomotion in early adulthood (P57-61). Next, rats were fitted with intravenous catheters and acquired cocaine self-administration. This was followed by assessment of cocaine self-administration according to a fixed and progressive ratio schedule of reinforcement and then during a 24-hour continuous access binge. Residents were less aggressive toward PH adolescent intruders compared to PH adults. Furthermore, PH adults displayed defensive and supine postures when attacked, whereas PH adolescents froze. Adolescent PH rats adapted their behavior from the first to last defeat by increasing freezing behavior, while SH rats decreased freezing. A greater percentage of SH rats and PH defeated rats acquired cocaine self-administration compared to PH controls. Defeated PH rats consumed more cocaine during progressive ratio schedules and during the binge compared to both PH controls and SH defeated rats. Greater attack-induced freezing after repeated defeats predicted escalated cocaine self-administration in adulthood. Thus, social defeat in adolescence, while different than during adulthood, still increased cocaine taking in PH, but not SH rats. Coping with attacks adaptively over repeated confrontations characterized adolescent PH rats and predicted adult cocaine taking. Support: NIH R01DA031734 (KAM), NIH F32DA032226 (ARB).

Social and hormonal factors in differences in stress responses between adolescents and adult rats. Cheryl McCormick, Brock University. The hypothalamic-pituitary-adrenal (HPA) axis is continuing to mature in adolescence, and pre-pubertal adolescents often show prolonged release of “stress” hormones (e.g., corticosterone) in response to a stressor relative to adults. In adults, stressors can also activate the hypothalamic-pituitary-gonadal (HPG) axis, which is not found in post-pubertal rats, in keeping with their low gonadal function. In turn, baseline testosterone concentrations are associated with individual differences in HPA responses to stressors in adults, with testosterone known to dampen HPA responses. In contrast, there is evidence that HPA function of pre-pubertal adolescents is insensitive to testosterone. Post-pubertal adolescents have higher plasma testosterone concentrations than pre-pubertal, but lower than adults. Yet, the extent and direction of difference between post-pubertal adolescents and adults in ACTH and corticosterone release in response to stress varies across types of stressors. I will describe: (1) our evidence that the HPA axis of post-pubertal adolescents is more responsive to repeated social stressors than are adults, although the reverse is true for the HPG axis, and (2) how testosterone alters HPA function in post-pubertal adolescents differently from both pre-pubertal adolescents and adults, evidence that suggests changes in neural substrates across development may have greater importance for HPA regulation than pre- to post-pubertal changes in testosterone concentrations. Lastly, I will discuss

how the “social brain” may be involved in the differential vulnerability of adolescents and adults to chronic stressors.

The long-term, sex-dependent effects of adolescent social stress on depressive-like behavior and stress-related neurocircuitry. Lukkes, Jodi L.; Norman, Kevin J.; Meda, Shirisha; Andersen, Susan L.; McLean Hospital and Harvard Medical School, Belmont, MA, USA. Exposure to adverse experiences during adolescence increases vulnerability to stress-related neuropsychiatric disorders of depression and anxiety during adulthood. Few preclinical studies have examined the sex-dependent effects of adolescent isolation-rearing on depressive-like behavior in adulthood, resulting in a poor understanding of the underlying mechanisms. Our previous studies have shown that adolescent isolation-rearing in male rats up-regulates corticotropin-releasing factor (CRF) type 2 receptors in the dorsal raphe nucleus (DR), prolongs CRF-mediated serotonin release in the nucleus accumbens, and increases social anxiety-like behavior in adulthood that can be attenuated with antagonism of CRF receptors in the DR. We hypothesize that isolation-rearing sensitizes a stress-related serotonergic pathway in the DR in a sex-dependent way that increases vulnerability to develop anxiety- and depressive-like behavior in adulthood. Therefore, we examined the long-term effects of isolation-rearing during adolescence on adult anxiety-like behavior using the elevated plus maze and depressive-like behavior using the learned helplessness triad (LH; escapable shock (ES), inescapable shock (IS), and no shock (NS) groups) in both male and female rats. The LH triad allows an in-depth characterization of multiple aspects of depressive-like behavior as each condition is mediated partly by separate neuronal circuits. Utilizing qRT-PCR, we also examined isolation-induced changes in CRF1 and CRF2 receptor mRNA expression in five subregions of the DR that have specific projections to stress-related forebrain regions. Adolescent isolation-rearing in both males and females increased anxiety-like behavior. Increased depressive-like behavior following adolescent isolation-rearing was observed in ES and NS males only, suggesting controllability and motivational deficits. This sex-dependent effect of isolation-rearing on depressive-like behavior indicates that perhaps a different type of social experience during adolescence is needed to induce depressive-like behavior in females. Isolation-rearing of males decreased CRF2 receptor mRNA expression, whereas group-rearing increased CRF1 receptor mRNA expression in the dorsal part of the DR. This region projects to several anxiety- and depression- related pathways, such as the medial prefrontal cortex and nucleus accumbens. These data suggest that adolescent isolation-rearing has sex-dependent, long-term effects on behavior and stress-related serotonergic systems that are implicated in the pathophysiology of neuropsychiatric disorders, such as depression and anxiety.

10:30 **Bench-to-Bedside Lecture: J.F. William Deakin**, University of Manchester, U.K. Finding new treatments for schizophrenia; behavior, biomarkers and clinical trials.

1:00-3:00 **Obsessive-compulsive disorder: Insights from animal models.** Chair: **Henry Szechtman; Richard Beninger.**

Understanding the OCD brain: using new technologies to build bridges between mice and humans. Susanne E. Ahmari, MD, PhD1**.** 1University of Pittsburgh, Translational Neuroscience Program, Center for Neural Basis of Cognition, Center for Neuroscience Program. Obsessive Compulsive Disorder (OCD) is a chronic, severe mental illness that affects 2-3% of people worldwide, yet the pathophysiology remains unclear. Though multiple lines of evidence indicate that dysregulation within cortico-striato-thalamo-cortical (CSTC) circuits is correlated with OCD, causation cannot be tested in humans. We therefore turned to an animal model system to gain insight into how abnormal CSTC activity leads to abnormal repetitive behaviors. We used optogenetic technology in mice to simulate CSTC hyperactivation observed in functional imaging studies in OCD patients. Mice were injected with AAV-channelrhodopsin-EYFP in orbitofrontal cortex (OFC), and implanted with fiberoptics in ventromedial striatum (VMS). 473nm stimulation of OFC-VMS projections (10Hz, 10msec, 10mW) yielded light-evoked electrophysiologic responses. 5 minutes of stimulation was performed daily for 5 consecutive days; behavioral measures included grooming and locomotor assessment using an open field chamber. Data was analyzed using repeated-measures ANOVAs and post-hoc tests. In vivo electrophysiology was performed to examine

electrophysiologic correlates of behavioral responses. Repeated hyperactivation of OFC-VMS projections over 5 days induced a progressive increase in repetitive grooming, a mouse behavior linked to OCD ($p<.05$). Increased grooming persisted for 2 weeks after cessation of stimulation ($p<.03$), and was reversed by chronic fluoxetine. Development of persistent grooming was correlated with increased evoked activity at OFC-VMS synapses ($p<.02$). No differences were observed in anxiety or prepulse inhibition. This is the first evidence that repeated hyperactivation of cortico-striatal projections directly generates OCD-like behaviors. Furthermore, repetitive grooming, once established, persists without further direct circuit hyperactivation, but is resolved using a treatment regimen effective in reducing OCD symptoms in a subset of patients. Finally, plasticity at OFC-VMS synapses correlates with the observed behavioral changes. These studies could offer novel insights into synaptic plasticity mechanisms that may underlie the development of maladaptive repetitive behaviors in OCD patients.

Mechanisms of polydipsia in rats: clues for understanding OCD. Richard J Beninger, Emily R Hawken. Queen's University at Kingston. Polydipsia is excessive non-regulatory drinking. Polydipsia has some of the characteristics of compulsive behaviors seen in obsessive-compulsive disorder (OCD) including a somewhat stereotyped repetitiveness and polydipsia can lead to physical distress including hyponatremia and water intoxication. Placing food-restricted animals on schedules of intermittent feeding can lead to schedule-induced polydipsia (SIP). We have observed significantly enhanced SIP in several rat models including: post-weaning social isolation, sub-chronic treatment with an NMDA glutamate receptor antagonist, and amphetamine sensitization. In learning tests using a Y-maze, we found that amphetamine-sensitized rats shifted towards using a response-learning strategy and away from using a place-learning strategy. Response-learning strategies have been associated with corticostriatal circuits and over-activity of orbitofrono- and prefrontocortical-striatal circuits has been implicated in OCD. We hypothesized that response-learning strategies in SIP-expressing rats would be associated with increased neuronal activation in the orbital and prefrontal cortex and possibly dorsal striatum. Immunocytochemical studies of FosB/ΔFosB revealed greater expression in the prefrontal and orbitofrontal cortex but not the dorsolateral striatum or CA1 region of the hippocampus in rats that showed strong SIP compared to rats that did not show SIP. Results reveal that animal models, in this case amphetamine sensitization, that lead to enhanced SIP also produce shifts in behavioral strategies that may reflect stronger activity in frontocortical-striatal circuits. Future studies will further refine understanding of the neural circuitry underlying OCD. Work with animals using a theory-driven behavioral neuroscience approach will continue to direct research on OCD. (Funded by the Ontario Mental Health Foundation).

Analysis and synthesis of compulsive checking: Indications that OCD is a disturbance of motivation. Szechtman, Henry. McMaster University. The quinpirole sensitization rat model of obsessive-compulsive disorder (OCD) measures spontaneous behavior in an open-ended situation where there are no explicit rewards or contingencies. This simulates the condition which challenges OCD patients; namely, how to behave in situations of uncertainty where the environment does not dictate the optimal response. As such, the quinpirole preparation is open to a rich and sophisticated analysis of the behaviors that constitute the observable symptoms of the disorder, and in particular, compulsive checking. In a series of studies we decomposed compulsive checking experimentally into three relatively independent functional components, all greatly exaggerated by quinpirole: (a) vigor of checking; (b) the focus on checking; and, (c) rest or "satiety" after a bout of checking. The appropriateness of this analysis was substantiated in a "synthesis" study in which these putative components were evoked experimentally by non-quinpirole treatments, and found to self-assemble into 'compulsive' checking as observed with quinpirole. The successful decomposition of compulsive checking in the animal model reveals what is "compulsive" behavior, namely, highly motivated performance but without apparent satiation. Thus, the

animal model findings suggest that compulsions of individuals with OCD should be considered as the output of a motivational system. Indeed, the insights from the completely independent analysis of compulsive behavior in the animal model converge with the recently proposed theory that OCD reflects a disturbance of a security motivation system. Supported by operating grants from the Canadian Institutes of Health Research (CIHR MOP-64424), Natural Sciences and Engineering Research Council of Canada (RGPIN A0544) and Ontario Mental Health Foundation.

Discovering macroscopic networks and their modulation in animal models of repetitive disorders. Christine Winter. Repetitive behaviors constitute isolated phenomena often preceded by so-called premonitory urges that are alleviated by the action of the repetitive action. Though incompletely understood, they are believed to be caused by disruptions within the basal ganglia-thalamo-cortical (BGTC) circuit and the dopamine system. Traditional treatment approaches are often associated with poor symptom alleviation, treatment resistance and side effects severe enough to require discontinuation of the treatment. To develop rationale driven therapeutic interventions the spatial and temporal disruption of the macroscopic function of distributed brain networks needs to be considered. We will here present an approach that uses different animal models of repetitive behavior in parallel to untangle the temporo-spatial disruption of the BGTC circuit and the dopamine system in the generation of repetitive behavior, i.e. the quinpirole rat model of compulsive behavior, the dopamine transporter overexpressing rat model of Tourette-Syndrome and the maternal immune activation rat model of schizophrenia. We will show how we test therapeutic interventions that directly target the origins of the distinct symptoms based on a thorough description of brain activity and biochemical abnormalities across the pathology models. Given its unique ability to target specific brain regions, we will show how deep brain stimulation (DBS) can be used to substantiate the pathophysiological and therapeutic relevance of BGTC circuit compartments. We will propose advancements to conventional DBS that also considers the temporal disruption of the macroscopic function of the BGTC circuits in the manifestation of repetitive behaviors. We will conclude that studies are mandatory that correlate neurotransmission or oscillatory activity and symptom presentation in order to provide the rationale for the development of feedback controlled treatment approaches capable of closed-loop intervention responsive to the targeted symptoms.

1:00-3:00 **Why sex hormones matter for behavior and brain health.** Chairs: **Elena Choleris, Liisa Galea.**

Estrogens and the aging brain: Maintenance functions of sex steroids in the female frontal cortex. E. Hampson. University of Western Ontario, London, ON, Canada. The role of estrogen in the maintenance of explicit memory has been studied extensively in post-menopausal women, through studies examining performance in women who are taking vs. not taking estrogen replacement therapy (with or without a progestogen, such as medroxyprogesterone acetate). Conjugated equine estrogens (CEE) have been the major focus of this work and memory tests employed are generally those that require the hippocampus and surrounding temporal cortex. A smaller body of literature suggests that the prefrontal cortex (PFC) may be a significant site of estrogen activity in the adult female brain, and that the loss of estrogen with aging in women may have implications for functions dependent on the PFC. This talk will describe studies from our laboratory and others that identify the PFC as an important target for estrogens. Working memory will be used as a prototypical function, and data will include behavioral, imaging, and molecular studies. An important question is how much of the decline in working memory usually attributed to aging is really due to endocrine changes associated with age. The 'dark side' of estrogen will also be discussed. Funded by the Canadian Institutes of Health Research and Natural Sciences and Engineering Research Council of Canada.

Molecular mechanisms underlying estrogenic memory enhancement. Frick, Karyn M. University of Wisconsin-Milwaukee, Dept. of Psychology, Milwaukee, WI USA. The classical mechanism through

which sex steroid hormones regulate gene expression involves the binding of a hormone-receptor complex to a hormone response element on the DNA, thereby requiring a direct interaction between hormone receptors and nuclear DNA. However, it has become increasingly well accepted that 17beta-estradiol and other sex steroid hormones can rapidly influence cellular function without direct receptor-DNA interactions. For example, we have shown that the effects of 17beta-estradiol on hippocampal function require interactions with neurotransmitter receptors, activation of cell signaling cascades, and facilitation of epigenetic processes such as histone acetylation and DNA methylation. This talk will briefly review our data showing that these non-classical mechanisms are necessary for 17beta-estradiol to enhance hippocampal-dependent object recognition and spatial memory in ovariectomized mice, and will provide a synthesis of these findings to date.

Rapid action of estrogens and their receptors in the brain: implications for learning. Elena Choleris1., Anna Phan 1,2, Jennifer Lymer1, Kelsy Ervin1, Christopher S. Gabor1. 1Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON, Canada, echoleri@uoguelph.ca, 2now at Department of Neuroscience, Scripps institute, FL, USA. In addition to their delayed and long-lasting genomic actions, estrogens can also act very rapidly via intracellular signaling non-genomic mechanisms. In studies with systemic treatments with 17□-estradiol to ovariectomized mice we have shown very rapid facilitation of various learning tasks: social recognition (SR), object recognition (OR), object placement (OP) and the social transmission of food preferences (STFP). Estrogen receptor (ER) □ and G-protein-coupled ER (GPER) predominantly mediate these effects. However we also found differences in specific ER-involvement in these tasks. Systemic ER□ agonist PPT rapidly enhanced performance in SR, OR, and OP, but impaired the STFP. GPER agonist G1 rapidly enhanced performance in SR, OR, OP and STFP. ER□ agonist DPN rapidly enhanced OP, impaired SR and did not affect OR and STFP. In other female mice that had not undergone the learning tasks we also found that estradiol rapidly increased dendritic spine density in CA1 hippocampus, (Golgi staining and biocytin single cell loading). Similarly, PPT and G1 increased, while DPN decreased or had no effects on CA1 dendritic spines. Hence, we infused the above treatments in the dorsal hippocampus of ovariectomized mice via implanted guide cannulae. The total time from treatment to end of testing was 40 min, thus tapping into the rapid effects of estrogens. 17□-estradiol, PPT and G1 rapidly improved performance in SR and OR recognition, PPT enhanced and G1 impaired OP tests, while DPN only improved OP. STFP was unaffected by dorsal hippocampal 17□-estradiol, suggesting the involvement of other brain areas. The role of the Lateral Amygdala in the STFP is being investigated. Then, using a Y-maze to minimize spatial information we determined that dorsal hippocampal 17□-estradiol still enhanced OR but not SR. Hence, dorsal hippocampal estrogens rapidly and directly enhance OR and OP while they enhance SR via associated spatial information processing. We subsequently showed that the Medial Amygdala may be involved in direct enhancing effects of 17□-estradiol on SR. Overall, we are identifying a network of brain regions specifically and interconnectedly implicated in estrogens' and ER's very rapid effects on various learning tasks. Funded by the Natural Sciences and Engineering Research Council of Canada.

Stroke neuroprotection in aging females: Beyond estrogen. Farida Sohrabji, Women's Health in Neuroscience Program, Dept of Neuroscience and Experimental Therapeutics, Texas A&M Health Science Center, Bryan TX 77807. Stroke is the 4th leading cause of mortality in the US. It occurs more often in the elderly and, within this demographic, more frequently among women than men. Animal models replicate this age and sex difference in stroke severity. Young female rats (5-6 months of age) have smaller infarct volumes as compared to middle-aged, acyclic females (10-12 months). This led to the hypothesis that poor stroke outcome in middle-aged females was related to the loss of estrogen during reproductive senescence. Estrogen treatment to ovariectomized young females (surgical menopause model) reduces infarct volume, which supported this hypothesis. Paradoxically, our studies show that estrogen treatment to middle-aged female rats actually increases infarct volume and exacerbates sensory motor deficits. The loss of estrogen-mediated neuroprotection with age suggests that other endogenous molecules may modulate the action of estrogen depending on the reproductive 'age' of the animal. Like steroid hormones, small non-coding RNA called microRNA exert broad control

over cell function. Unlike classical hormone action, miRNA act as translational repressors by binding the 3' UTR of target genes. QPCR analysis indicated that cortical levels of Let7f and Mir1 were elevated in middle-aged animals as compared to young females. Since Let7 targets a number of genes that promote survival such as BDNF, and IGF-1, we hypothesized that antagomirs (inhibitors) to this miRNA would promote growth factor synthesis and, by extension, promote post stroke neuroprotection. Anti-Let7f, injected ICV after stroke significantly reduced infarct volume and improved sensory motor function in young females. However, this antagomir was ineffective in reducing infarct volume in males and in ovariectomized females, and paradoxically increased infarct volume in middle-aged females, suggesting that endogenous estrogen levels are crucial for antagomir effects. In an effort to identify a therapeutic target for stroke in this middle-aged group that is not affected by endogenous hormone levels, we next compared the expression profile of circulating microRNA post stroke in young and middle aged males and females. Mir363 was found to be elevated in young animals in the acute stroke phase, and continues to elevate in young females until 5d post stroke. To mimic this profile, mir363 mimetics were injected IV to middle aged females post stroke. Our results show that the mimetic reduced infarct volume and improved performance on a sensory motor task in this group. These studies underscore the value of age and sex comparisons in developing novel stroke therapeutics. Supported by R01NS074895 and R01AG042189.

Caveats and pitfalls for studying the influence of sex and sex hormones in neuroscience. Liisa A.M. Galea University of British Columbia**.** Although sex differences exist in many brain diseases, research targeting sex as a factor in brain health has been scarce. Anytime a sex difference is seen in any trait, disease manifestation or treatment this suggests that sex hormones are involved. Sex hormones can influence behavior and brain either early in life (organizational effects) or later in life (activational effects). While there are movements afoot to encourage investigators to use both males and females in their research, the addition of both sexes can be fraught with methodological issues. Pheromones from either sex can significantly influence behavior and neuroplasticity. Menstrual and estrous cycle phase influence brain activation, behavior and cognitive performance in females. Therefore, ignoring the necessity to house animals separately or track estrous/menstrual cycle can be detrimental to a better understanding of the influence of sex and sex hormones. Furthermore, merely the addition of both sexes is not enough to advance medical and scientific knowledge. The use of sex needs to be considered in the statistical analysis and examples will be given on the consequences of grouping males and females together on data analyses and interpretation. Much has been made in the literature on the need for individualized medicine to further advance treatment. I will discuss the fact that studying and analyzing sex differences in our work is a necessary (first) step to personalized medicine. I firmly believe that only by not ignoring sex and sex hormone differences in outcomes of preclinical and clinical studies can we significantly advance treatments and health outcomes that will ultimately improve the lives of women and men.

3:30-5:30 **Standardization of Rodent Behavioral Testing: Where we've been, and where we're going.** Chair: **Abbe H. Macbeth.**

Standardized Assays for Mouse Models of Neurodevelopmental Disorders. JL Silverman. MIND Institute and Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, CA 95817 USA. Neurodevelopmental disorders (NDDs), including intellectual disability (ID) and autism spectrum disorder (ASD), are pervasive, lifelong disorders for which pharmacological interventions are not currently available. Animal models are indispensable in the enterprise of elucidating causes of, and treatments for, NDDs. These disorders were long thought to be medically untreatable, on the assumption that brain dysfunctions were irreversibly hardwired. Dysregulation of the excitatory/inhibitory balance in the brain has been hypothesized as a possible cause of ASD and some ID syndromes. Reducing excitatory glutamatergic transmission, and/or elevating GABAergic inhibition, is posited to normalize the excitatory/inhibitory balance and reverse relevant behavioral phenotypes. One objective of our research group is to test the hypothesis that modulating excitatory/inhibitory balance could reduce high levels of repetitive behavior, and improve sociability and cognition in standardized assays with high face validity. Results shown in this presentation will focus on

effects of mGluR modulators and a GABAB agonist compound. Our findings promote the use of behavioral standardization to increase reproducibility within and across laboratory settings and advance therapeutic development. Supported by the UC Davis MIND Institute.

You want me to do what with your mouse? Tales of "standardized testing" from the behavioral testing core facility at UCSD. Charles J. Heyser. Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093. In order to determine the role of specific neural pathways, neurochemical events and/or genes on specific behaviors, assays of animal behavior need to be valid, reliable and replicable across laboratories. However, in the 1907 publication of "The Dancing Mouse", Yerkes stated that, "The nature of the modifications which are wrought in the behavior of an organism varies with the methods of training" (p. 239). It is therefore not surprising that there have been a number of publications in the last 2 decades demonstrating that the same behavioral procedures do not always produce consistent results in the same rodent lines across different laboratories. These results serve to highlight the complex nature of behavior, the laboratory environment and their interaction. As a result, many researchers have indicated the need for a "standardized" behavioral test battery. It is clear that standardization has many benefits and is often the best place to begin any experiment. However, in my talk I will draw a distinction between procedural standardization and behavioral standardization. For example, to observe alterations in learning after knockout or transgenic manipulation, it is critical that the wild-type control mouse be able to learn the task. To this end, we have shown previously that the parameters of an avoidance task had to be modified to accommodate learning in the specific background strains of mouse (Heyser et al., 1997). In addition, the contribution of inherent variability (i.e., the reality that some behaviors are more variable than others) will be discussed in the context of how one might standardize rodent behavioral testing. Special attention will be given to the development of standardized procedures, the use of automated equipment, the potential advantages of core behavioral testing facilities, and the critical need for appropriate control groups to determine if we are indeed measuring what we think we are measuring.

Motherhood in many contexts: Standardization of maternal behavior testing. Danielle S. Stolzenberg1, 1 University of California, Davis. Mothering involves complex behavioral modifications aimed at ensuring the survival of progeny. The neurobiology of maternal behavior has been extensively studied in rats and mice. Rodent pups are born with limited sensory and motor capabilities, and rely exclusively on these maternal caregiving behaviors for their survival. Female rodents learn to care for infants and their caregiving behaviors vary with environmental context. Critical questions are how do new mothers adapt their behavior in different environmental contexts and how do these altered patterns of care promote the adaptive development of offspring? To address these questions methods for the standardization of maternal behavior testing in different environmental contexts will be discussed.

"Standardized "tests and the problem of reliability and validity in mouse behavioural bioassays. Richard E. Brown**.** Department of Psychology and Neuroscience**,** Dalhousie University**,** PO BOX 15000, Halifax, Nova Scotia**,** CANADA B3H 4R2. A behavioural phenotype is the observable behavior characteristic of humans or mice with a particular genetic or chromosomal disorder. The behavioural phenotype of a transgenic mouse model will differ from that of the wild-type control, reflecting the neuro-genetic changes in the genetically altered mouse. In order to determine reliable and valid behavioural phenotypes, we must ensure that the "standardized" tests that we use are measuring what we intend to measure in order to make conclusions about the neural and/or genetic mechanisms underlying anxiety, learning, memory and other cognitive processes (Schellinck, et al 2010 Advances in the Study of Behavior, 41, 255-366; O'Leary, et al., 2013. Behav. Gen. 43, 34-50). I will discuss examples of how apparatus design and test procedure can effect experimental results. I will also discuss how confounding factors in mouse behavioural bioassays can lead to erroneous conclusions in studies designed to develop new drugs. Finally I will suggest some ways to ensure that the results of behavioural tests are reliable and valid.

3:30-5:30 **Neurobiological consequences of drug exposure during adolescence: Mechanisms and long-term effects.** Chairs: **Arturo R. Zavala, Sergio D. Iñiguez.**

Juvenile administration of concomitant methylphenidate and fluoxetine alters behavioral reactivity to reward and aversive stimuli and disrupts ventral tegmental area gene expression in adulthood. Carlos A. Bolaños-Guzmán, Lyonna F. Alcantara, Eric Parise, Omar K. Sial**.** Department of Psychology and Program in Neuroscience, Florida State University, Tallahassee, FL, 32306. There is a rise in the concurrent use of methylphenidate (MPH) and fluoxetine (FLX) in pediatric populations. However, the long-term neurobiological consequences of combined MPH and FLX treatment (MPH; FLX) during juvenile periods are unknown. Saline (VEH), MPH, FLX, or MPH+FLX was administered to juvenile Sprague Dawley male rats from postnatal day 20-34, and their reactivity to reward- and mood-related stimuli 24 h or 2 months after drug exposure was assessed. Biochemical changes within the ventral tegmental area (VTA) after MPH, FLX, or MPH+FLX were assessed. MPH+FLX treatment enhanced sensitivity to drug (i.e., cocaine) and sucrose rewards, as well as anxiety (i.e., elevated plus maze)- and stress (i.e., forced swimming)-eliciting situations when compared with VEH-treated rats. MPH+FLX exposure also increased mRNA of ERK2 and its downstream targets cAMP response element-binding protein (CREB), BDNF, c-Fos, early growth response protein-1 (Zif268), and mammalian target of rapamycin (mTOR), and also increased protein phosphorylation of ERK2, CREB, and mTOR 2 months after drug exposure when compared with VEH-treated rats. Blocking ERK2 activity using herpes simplex virus-mediated gene transfer within the VTA rescued the MPH and FLX-induced behavioral deficits seen in the forced-swimming task 2 months after drug treatment. These results indicate that concurrent MPH+FLX exposure during preadolescence increases sensitivity to reward-related stimuli while simultaneously enhancing susceptibility to stressful situations, at least in part, due to long-lasting disruptions in ERK signaling within the VTA.

Adolescent prescription drug exposure effects on social play behavior and frontal cortex-dependent reward learning. Alicia Izquierdo**.** UCLA, Department of Psychology, Brain Research Institute**.** One learns to predict future outcomes through novel experiences and social interactions during adolescence. Likely due to this developmental period's minimization of risk and punishment processing, the net behavioral effect promotes exploration. The frontal cortex is responsible for such important executive functions including flexible reward learning and prediction of reward outcomes. In the adult, we recently found that markers of immune dysregulation in the frontal cortex during protracted methamphetamine withdrawal are significantly correlated with reward choices. Interestingly, we have new evidence that drug-naïve adolescents are indistinguishable from drug-experienced adults on those choices (unpublished); an effect that suggests reward learning has a distinct developmental trajectory. The introduction of commonly prescribed methylphenidate (MPH) or fluoxetine (FLX) in adolescence may also have a long-lasting effect on the development of the frontal cortex and reward learning. To our knowledge, there has not yet been a systematic comparison of the effects of these drugs in adolescence on social interactions and frontal cortex-mediated learning. Thirty-two male and female Long-Evans rats were randomly assigned to MPH (1 mg/kg or 3 mg/kg), FLX (5 mg/kg or 10 mg/kg), or saline treatment, and compared with methamphetamine treatment (escalating .3mg/kg – 3 mg/kg), for 15 d beginning in postnatal day 35, a period for rats that is believed to mark early-to-middle adolescence. During drug treatment, pairs of rats were assessed for their social play behavior on Day 0, 7, and 15 of drug treatment. The rats were then tested on discrimination and reversal learning, the latter known to depend on the integrity of the frontal cortex. Unexpectedly, we found a marked sex difference in rates of learning with female rats learning more slowly than male rats. We also found a significant interaction of drug treatment group x session during learning, with MPH producing the slowest learning and most aberrant social play behavior. Ongoing experiments are aimed at determining the mechanism for these effects and

assessing correlates of this learning using measures of synaptic remodeling and inflammation in frontal cortex, amygdala, and striatum.

Neurobiological consequences of nicotine exposure during adolescence: Short and long-term effects. Laura E. O'Dell, Luis A., Natividad, Luis Carcoba**.** Department of Psychology, The University of Texas at El Paso, El Paso, TX. Rationale: It is widely accepted that initial experimentation with tobacco occurs during adolescence, and that early tobacco use promotes nicotine dependence later in adulthood. Also, adolescents often use tobacco products as a weight loss tool. However, it is unclear whether the weight suppressant effects of nicotine are similar during adolescence or in adults that were exposed to nicotine during adolescence. To address these issues, behavioral studies in our laboratory have compared the rewarding and weight suppressant effects of nicotine in adolescent, adult, and adult rats that were exposed to nicotine during adolescence. Methods: We used a model of nicotine self-administration (SA) whereby rats were given 23-hour access to increasing doses of nicotine separated by brief periods of drug abstinence. Adolescent and adult rats were first trained to perform operant responses for food and water in the SA chambers and were implanted with a jugular catheter for intravenous SA of nicotine. An additional group of adolescents were pretreated with nicotine via osmotic pumps (4.2 mg/kg/day) for 14 days and received catheters later in adulthood. Rats were given access to nicotine SA for 3, 4-day cycles whereby the dose of nicotine was increased between each cycle as follows: 0.03, 0.06, 0.09 mg/kg/0.1 ml infusion given over two cycles. Each cycle was separated by a forced period of abstinence for 3 days. Results: Our findings revealed that nicotine intake was highest in adolescents, intermediate in adults that were exposed to nicotine during adolescence, and lowest in drug-naive adults. Adolescents displayed the highest food-intake and weight gain during the SA sessions as compared to the other groups. Exposure to nicotine during adolescence blocked the food- and weight-suppressant effects of nicotine later in adulthood as compared to naïve adults that displayed robust weight suppressant effects of nicotine. Conclusions: Our results suggest that are long-lasting metabolic consequences of adolescent nicotine exposure, including a reduction in the food-intake suppressant effects of this drug. These findings have clinical implications towards treating adolescent smokers with nicotine replacement therapy, as this approach may produce detrimental long-term consequences on food intake and weight control later in adulthood. Ongoing studies in our laboratory are examining the mechanisms by which adolescent nicotine exposure promotes long-term vulnerability to tobacco use.

Amphetamine in adolescence disrupts prefrontal cortex development. Cecilia Flores, PhD**.** McGill University, Montreal, Quebec, Canada**.** Initiation of drug use during adolescence is a strong predictor of both the incidence and severity of addiction throughout the lifetime. Intriguingly, adolescence is a period of dynamic refinement in the organization of neuronal connectivity, in particular medial prefrontal cortex (mPFC) dopamine circuitry. The guidance cue receptor, DCC (deleted in colorectal cancer), is highly expressed by dopamine neurons and orchestrates their innervation to the mPFC during adolescence. Because amphetamine in adolescence regulates DCC expression in dopamine neurons we hypothesized that drugs in adolescence induce their enduring behavioral effects via DCC-mediated disruption in mPFC dopamine development. In a series of studies we investigated the impact of abused doses of amphetamine during adolescence on the development of mPFC dopamine connectivity in mice. We compared these effects to those induced by an identical amphetamine regimen given to adult mice. We found that amphetamine in adolescence, but not in adulthood, leads to an increase in the span of dopamine innervation to the mPFC, but a reduction of presynaptic sites present on these axons. Amphetamine treatment in adolescence, but not in adulthood, also produced an increase in salience attribution to a previously drug-paired context in adulthood. Remarkably, the effects of amphetamine in adolescence on both mPFC dopamine connectivity and on behavior require DCC signaling within dopamine neurons. We are currently investigating how amphetamine-induced disruption of DCC signaling

within dopamine neurons leads to their aberrant connectivity in the mPFC. Our recent results suggest that amphetamine induces regrowth of DCC-expressing dopamine axons from striatal regions to the mPFC by promoting target recognition errors between these axons and their netrin-1-expressing postsynaptic partners. We also find that alterations in mPFC DA innervation induce structural reorganization of mPFC local circuitry, influencing cognitive processing in adulthood. Drugs of abuse in adolescence may induce their detrimental behavioral consequences by disrupting mesocortical dopamine development through alterations in the DCC signaling cascade.

6:00-8:00 **Poster Session 2:**

1. **Perturbations in prefrontal-ventral striatal mediated cognitive functions, dopaminergic innervation and testosterone associated with aging.** Tomm RJ, Ma CQ, Low KL, Tse MT, Grist MM, Floresco SB, Soma KK. Department of Psychology and the Brain Research Centre, The University of British Columbia, Vancouver BC, Canada. The process of aging is often associated with impairments in cognition, decision making, and executive function. These impairments have been linked with declining dopamine (DA) synthesis in the prefrontal cortex (PFC). Interestingly, levels of circulating testosterone (T) also decline during aging, coinciding with the onset of cognitive dysfunction. T regulates DA synthesis and/or action in the ventral tegmental area (VTA), nucleus accumbens (NAc), and PFC. Thus, changes in levels of circulating T during aging might affect cognition via the DA system. In the current study, we compared young adults (5 months) and aged (22 months) male rats (Fischer 344/Brown Norway hybrid) on three cognitive tasks mediated by different regions of the frontal lobes and the NAc. Working memory was assessed with a delayed win-shift version of the radial arm maze, and aged rats displayed a marked impairment in performance. The qualitative nature of this impairment resembled that induced by medial PFC inactivation. Probabilistic learning and flexibility were assessed with a probabilistic reversal learning task. Here, aged rats completed more reversals than young rats and also displayed an increased sensitivity to reward and negative feedback. This suggests that rather than keeping long-term action-reward histories, the aged rats were driven by more immediate feedback, again suggestive of impaired PFC function. Cognitive flexibility was assessed with a strategy set-shifting task. Here, aged rats were impaired, relative to young rats, during initial learning of a visual cue discrimination. During a shift to an egocentric spatial response rule, aged rats showed a selective impairment in acquiring the novel strategy, a function mediated by PFC dopamine D1 receptors and medial thalamic-NAc circuitry. Subsequent immunohistochemical and steroid assays revealed that, compared to young rats, aged rats showed decreased levels of the DA-synthesizing enzyme tyrosine hydroxylase as well as of T in the NAc. These data provide a framework and a potential site of action for future experimental work exploring the interaction of T and DA on cognitive function during aging and suggest that perturbations in the neurochemical and androgen regulation of prefrontal cortical-ventral striatal interactions may contribute to cognitive dysfunction associated with aging.

2. **Behavioral effects of inactivating DA receptors in the caudate-putamen and nucleus accumbens of young rats.** Mohd-Yusof A, Rudberg KN, Moran A, Razo J, Macedo E, Eaton SE, Crawford CA, McDougall SA. Department of Psychology, California State University, San Bernardino. Inactivating DA receptors in the caudate-putamen (CPu) differentially affects the locomotion of adult and young rats. In adult rats, microinjecting the irreversible receptor antagonist EEDQ into the CPu blocks the locomotion produced by both direct (NPA) and indirect DA agonists. In contrast, EEDQ potentiates rather than attenuates the DA agonist-induced locomotion of young rats. Ontogenetic changes in DA receptor dynamics may be responsible for these age-dependent behavioral differences. Namely, the percentage of high affinity D2 receptors ($D2^{High}$ receptors) is elevated in

young rats relative to adults, and these differences are amplified after EEDQ treatment. Thus, in young rats, but not adults, EEDQ-induced increases in the percentage of $D2^{High}$ receptors may more than compensate for the overall loss of DA receptors. The purpose of the present study was to determine if EEDQ causes a similar pattern of behavioral effects when infused into the nucleus accumbens (NAcc) of young rats. And, second, to determine whether the ability to potentiate or attenuate DA agonist-induced locomotion is influenced by the amount of striatal and accumbal tissue affected by EEDQ. On PD 17, EEDQ (100 µg) and DMSO were bilaterally infused into the NAcc or CPu at a volume of 0.25, 0.5, or 0.75 µl. After 24 h, rats were given bilateral infusions of vehicle or NPA (10 µg) and behavior was assessed for 40 min. Young rats exhibited a significant increase in locomotion after NPA was infused into the NAcc or CPu. Microinjecting 0.75 µl EEDQ into the CPu potentiated this heightened locomotor response, whereas rats given a lesser volume of EEDQ (0.25 µl) were unaffected. Administering EEDQ (0.25–0.75 µl) into the NAcc did not potentiate the NPA-induced locomotion of young rats. Autoradiography showed that EEDQ caused a substantial reduction in the total number of D2 receptors in the CPu and NAcc, with 0.75 µl EEDQ producing a greater area of receptor loss than lesser volumes. In terms of the CPu, we believe that the potentiated locomotor response was caused by an EEDQ-induced increase in the percentage of $D2^{High}$ receptors. The fact that administering EEDQ into the NAcc did not attenuate DA agonist-induced locomotion suggests that the percentage of $D2^{High}$ receptors was elevated, but this receptor-mediated effect was apparently insufficient to support a potentiated locomotor response. When considered in terms of past studies showing that EEDQ fully attenuates the DA agonist-induced behaviors of adult rats, our results indicate that DA receptor dynamics and DA-mediated behavioral responsiveness differs substantially between the preweanling period and adulthood. [Funded by NIH grants MH102930, GM100829, and DA033877]

3. **Behavior features and response to naltrexone among outbred Wistar rats from different suppliers.** Shima Momeni, Lova Segerström and Erika Roman. Neuropharmacology, Addiction and Behaviour, Department of Pharmaceutical Bioscience, Uppsala University, Uppsala, Sweden. Naltrexone is one of the main pharmacotherapies used for alcohol use disorders. Clinical and preclinical reports reveal large individual differences and variance in the effect of naltrexone. Genetic factors and early life environmental factors are of importance for the outcome of naltrexone treatment. Alcohol intake and opioid peptide levels in outbred Wistar rats are different depending on supplier. Also, behavior characteristics in outbred Wistar rats have shown to be different depending on supplier. However, little is known about the impact of suppliers on the effect of naltrexone. The present work aimed to follow up on previous characterizations of Wistar rats from different suppliers by using the combination of an open field test and a Y-maze. Further, the study aimed to study the impact of suppliers on the effect of naltrexone. 60 outbred male Wistar rats from Harlan Laboratories B.V., Horst, The Netherlands (RccHan™:WI), Taconic Farms A/S, Ejby, Denmark (HanTac:WH) and Charles River, GmbH, Sulzfeld, Germany (Crl:WI) were tested in the open field test followed by the Y-maze. The animals were then given access to alcohol using a two-bottle free-choice paradigm with intermittent 24 h access to 20% alcohol and water for three consecutive days per week. After six weeks of voluntary alcohol intake, all animals were treated with naltrexone (0.03 mg/kg, 0.3 mg/kg or 3.0 mg/kg s.c.) and saline using a latin square design. Alcohol intake was measured 30 min, 2 h and 24 h after alcohol access. The Crl:WI animals showed the highest activity both in the open field test and the Y-maze. This group also spent the most time in the inner circle of the open field and showed least time of immobility compared to RccHan™:WI and HanTac:WH. However, no difference in correct alternations in the Y-maze was found between the groups. All groups established a stable alcohol intake; highest in RccHan™:WI. Naltrexone treatment resulted in a general decrease in alcohol intake. A detailed analysis revealed time- and dose-dependent effects. All groups showed

reduced alcohol intake after 30 min compared to saline. After 2 h no difference compared to saline was detectable in the Crl:WI animals, whereas a lower alcohol intake was found in HanTac:WH and RccHan™:WI animals. No naltrexone effect was seen after 24 h in any of the groups. Rats from different suppliers show different behavior features and also respond differently to naltrexone. Results from the present study emphasize the supplier as an important factor to consider when performing pharmacological studies. Funding: the Alcohol Research Council of the Swedish Alcohol Retailing Monopoly (SRA) and the Facias Foundation.

4. **Systemic modulation of dopamine D2/D3 receptors revert orbitofrontal neurophysiological neural correlates of risk preference in a rodent gambling task of decision-making under uncertainty.** Vasco Galhardo[1,2], Helder Cardoso-Cruz[1,2], Clara Monteiro[1,2], Margarida Dourado[1,2]. 1. Departamento de Biologia Experimental, Faculdade de Medicina, Universidade do Porto, 4200-319 Porto, Portugal. 2. Instituto de Biologia Molecular e Celular - IBMC, Universidade do Porto, 4150-180 Porto, Portugal. Dopaminergic signaling in orbitofrontal cortex (OFC) is thought to be critical for sustaining the neural representations of events critical for risk assessment during decision-making processes. It has been recently described that chronic pain patients and animal models of pain present disrupted risk assessment in emotion-based decision tasks under ambiguity such as the Iowa Gambling Task or the Rodent Gambling Task (RGT). Moreover it has also been shown that severe stressful conditions such as chronic pain, cause morphological and neurophysiological changes in prefrontal areas. However, it remains unclear whether pain-related changes in local OFC networks depend on dopaminergic modulation. In this study, we investigated whether the pharmacological modulation of D2r receptors activity alters pain-related abnormal risk-assessment and OFC neural representation during performance in the RGT probe session of decision-making under ambiguity. Briefly, the RGT is a two-lever free choice task in which naïve animals are exposed to new and uncertain reward probabilities associated with the two levers: over 90 trials the animals explore the contingencies and express a preference for either the low risk (1 food pellet at 0.9 chance) or the high risk lever (3 food pellets, 0.3 chance). Our previous studies have shown that control animals prefer the low-risk lever, while OFC-lesioned or animal models of pain prefer the high risk lever. To study the effect of dopamine modulation in the neurophysiological correlates of RGT performance, we implanted intracranial matrices of 8 tungsten electrodes in awake freely moving rats, and recorded the neural activity of populations of neurons in the OFC during performance in the RGT. Recordings were performed during the RGT training phase and during the testing probe sessions of risk assessment, and were repeated before and after the induction of the CFA model of inflammatory pain. We compared the behavioral performance and neurophysiological activity profile after the systemic or intra-OFC administration of either saline, D2/D3r agonist quinpirole (0.05 mg/ml) or D2/D3 antagonist raclopride (0.05 mg/ml). Our results show that both drugs disrupt normal performance in control animals, but systemic raclopride restores preference for the low risk lever in CFA animals. Intra-OFC administration was only able to partially reverse the impaired performance. The cluster analysis of OFC neural correlates shows that raclopride restores single lever specifity. Supported by FCT Grants SFRH/BD/70522/2010, SFRH/BPD/92203/2013 and PTDC/NEU-SCC/1516/2012.

5. **Assessing the effects of light dark manipulation and caffeine exposure on zebrafish sleep behavior.** Kanza M. Khan[1], Natalie R. Lodinger[1], Adam D. Collier[1], Erika M. Caramillo[1], David J. Echevarria[1]. [1]University of Southern Mississippi. Zebrafish (*Danio rerio*) have been gaining popularity as a model organism in neurobehavioral research over the past several decades. This small teleost fish possess several of the same neurotransmitter and neuropeptides that are found in rodent models and humans. As such, they provide valuable insight in to the underpinnings of addiction, learning,

memory and sleep behaviors. Previous sleep behavior research in zebrafish has focused on individual behavior in response to varying environmental stimuli. In this report we assessed sleep and wake behavior within groups of three fish to alleviate the stress effects of being removed from the shoal. Sleep and wake behavior of the groups were analyzed following three sleep-wake cycle manipulations: (1) constant light conditions, (2) constant dark conditions, and (3) constant light conditions, paired with the administration of an adenosine antagonist (caffeine). Following each sleep-wake cycle manipulation, the cohort of animals was transferred to a separate apparatus for either novel tank dive testing, or for cortisol analysis. We report a decrease in total sleep time following exposure to conditions in which animals were exposed to either constant light, or constant light paired with caffeine administration. Univariate ANOVA revealed a significant difference in the amount of time spent in the top region of the novel tank ($F(2,14)=98.8$, $p<0.001$). Animals in the constant light condition and in the caffeine plus constant light condition exhibited more anxiety like behaviors; exposure to constant dark resulted in a decrease in the number of anxiety-like behaviors produced. Cortisol expression was unchanged in animals exposed to constant light, but was significantly elevated in animals exposed to caffeine and constant light.

6. **The microbiota regulates amygdaloid volume and dendritic length.** Pauline Luczynski [1], Gerard Clarke [1,2], Fergus Shanahan [1], Timothy G. Dinan [1,2], and John F. Cryan [1,3.] [1] Alimentary Pharmabiotic Centre, University College Cork. [2] Department of Psychiatry, University College Cork. [3] Department of Anatomy and Neuroscience, University College Cork. Increasing evidence points to a role of the microbiota in the regulation of brain and behaviour. Germ-free (GF) mice (mice grown up without any exposure to microorganisms) are an important tool to assess if the microbiota is involved in key brain functions. We have previously shown that GF mice exhibit an exaggerated hypothalamic-pituitary-adrenal (HPA) axis response to an acute stressor and reduced anxiety-like behaviour. The amygdala is an important structure known to regulate fear and anxiety in the brain.While the mechanisms underlying how the absence of microbiota alters stress responsivity remain unclear, those that implicate the amygdala are likely targets. Several studies have documented stress-induced expansion in dendritic material and volume of the amygdala. It is unclear if the microbiota may play a role in such responses. Thus, the aim of the present study was to determine if the volume and dendritic morphology of the amygdala differ in GF compared to conventionally colonized (CC) mice. Stereological measures of well-defined subregions of the amygdala revealed significant expansions of the basolateral (BLA), lateral (LA) and central (CeA) nuclei in GF versus CC mice. We also investigated the effect of GF status at the level of single excitatory (pyramidal-like) and inhibitory (stellate) neurons in the BLA by measuring the length and branching of Golgi-stained neurons with morphometric software. In GF mice, pyramidal-like neurons were significantly elongated but did not show increased branching. Stellate neurons from GF animals showed a similar hypertrophy of dendritic material. These findings suggest that the presence of microbiota is critical for normal neurodevelopment of the amygdala and that neural remodelling along the brain-gut-microbiota axis could contribute to the altered stress-responsivity observed in GF animals. *The authors are funded by Science Foundation Ireland (SFI), through the Irish Government's National Development Plan in the form of a centre grant (Alimentary Pharmabiotic Centre Grant Number SFI/12/RC/2273).*

7. **From reward prediction error to dopamine hypothesis of psychosis: Insights from Akt1 mutant mice and schizophrenic patients.** Wen-Sung Lai [1, 2, 3], Ching-Chen [1], Hung-Hsiang Liu [1], Ya-Wen Liu [1], Chia-Tzu Li [1], Yao-Chu Chen [1], Chih-Ming Liu [4], Yung-Fong Hsu [1, 2, 3.] [1] Department of Psychology, National Taiwan University, Taipei, Taiwan. [2] Graduate Institute of Brain and Mind Sciences, National Taiwan University, Taiwan. [3] Neurobiology and Cognitive Science Center, National Taiwan University, Taiwan. [4] Department of Psychiatry, National Taiwan University Hospital, Taipei,

Taiwan. Making appropriate decisions involves the ability to update information of alternatives from previous experiences. In particular, the updated reward prediction error (RPE), a discrepancy between the predicted and actual rewards, is regarded as being encoded by dopamine (DA) neurons. Abnormalities in the DA system (or the DA hypothesis) have long been implicated in the explanatory context of schizophrenia (SZ). Specifically, dysregulation of DA systems could alter the appraisal of stimuli through a process of aberrant salience and eventually lead to psychosis. Thus the assessment of RPE could provide a potential behavioral index for dopaminergic activity in the brain that allows for the evaluation of psychosis. Taking advantage of rewarding tasks and model-fitting approach, we tackled this issue in both mutant mice and SZ patients. In the mouse studies, given the involvement of AKT1 (PKB alpha) in the pathogenesis of SZ and the importance of AKT1 in the DA downstream signaling cascade, male Akt1 mutant mice and their wild-type (WT) littermate controls were used to examine the role of Akt1 in the regulation of DA sensitivity, motivational salience, and reward-based choices. In a series of behavioral tasks, we found that (1) Akt1-/- mutant mice reveal a sex- and region-specific effect in the regulation of DA-dependent behaviors and methamphetamine sensitivity; (2) Akt1+/- mutant mice (HET) attributed motivational salience to the lever-CS after Pavlovian-conditioned pairing as WT but they learned the 2-choice dynamic foraging task faster than WT; (3) HET displayed a relatively efficient method of updating reward information from the environment during the acquisition phase of the two natural reward tasks and the reverse section of the dynamic foraging task. Our model-fitting results further revealed that HET update their reward values more rapidly and have more exploratory decisions than WT. These results indicate that Akt1 deficiency modulates natural reward learning and RPE. In the human study, adopted from our mouse task, we developed a dynamic reward task using a card-choosing scenario. SZ patients with low and high psychosis and healthy controls were recruited to perform this feedback-based task to receive money as rewards. Interestingly, our model-fitting results revealed that both psychosis groups show higher learning rates and more exploratory decisions as we reported previously in Akt1 mutant mice. We also found that the degree of exploration increases with the severity of the psychotic symptoms obtained from the PANSS subscores. Collectively, our studies demonstrated an avenue to investigate RPE in both mutant mice and SZ patients and provided a potential link from a genetic deficiency, to neurobiological abnormalities, to higher cognitive functions. Further studies on the emotional regulation of RPE and its related brain activities are in progress. Grant support: Grant numbers 102-2420-H-002-008-MY2 & 102-2628-H-002-003-MY3 from the Ministry of Science and Technology in Taiwan, NTU Hospital grants 102-053 and 104-034, and grants of Drunken Moon Lake Integrated Scientific Research Platform and Aim for Top University Project from NTU.

8. **Valproic acid improves anxiety-like behavior and amphetamine hyper-reactivity in isolation reared trait anxiety rats but reverses the benefits of environmental enrichment.** Donaldson, S.T.; Buteme, J.; Romero, V.; Lusse, J. Developmental and Brain Sciences, Psychology Department, University of Massachusetts Boston, Boston, MA 02125 USA. Valproic acid (VPA), a deacetylase inhibitor, has been shown to improve functioning in a number of animal models of early life stress (ELS) and mood disorders. The enriched environment (EE) also promotes recovery following ELS, anxiety and depression working at least through epigenetic mechanisms. In the present study, we determined the interaction of VPA with housing environment using 8th generation outbred trait anxiety animals bred along high (HAn) and low anxiety (LAn)-like behavior lines. Animals were housed for 30 days in EE, standard (SE) or isolated environments (IE), tested for anxiety and amphetamine sensitivity, given a 2-week VPA treatment (7 mg/ml) in drinking water, and re-tested on each of the behavioral measures. Results indicate that HAn animals reared in IE and SE showed greater anxiety-like behavior on the elevated plus-maze and open field, and hyper-activity to amphetamine, relative to HAn EE and all LAn groups. VPA *decreased* the benefits of EE but significantly improved the adverse

effects of IE on anxiogenic tests and amphetamine-induced locomotion. Immunohistochemical analysis of corticotropin-releasing hormone (CRH)-immunoreactivity in the central amygdala revealed a significant decrease in CRH-ir in LAn EE-reared rats compared to HAn EE. Collectively, the data suggest benefits of EE and VPA treatment in modulating trait anxiety and isolation rearing behavioral consequences. Moreover, the EE shifts in emotional responding and drug-sensitivity likely work through mechanisms other than regulation of CRH.

9. **Social buffering enhances extinction of fear response in male rats.** Yasushi Kiyokawa[1], Kaori Mikami[1], Yukari Takeuchi[1], Yuji Mori[1]. [1]Laboratory of Veterinary Ethology, The University of Tokyo, Tokyo, Japan. In fear extinction, the fear responses to the conditioned stimulus (CS) are decreased after the extinction training. We have reported the social buffering phenomenon in male rats that the presence of a non-conditioned conspecific animal (associate) mitigated fear and stress responses induced by the auditory CS. Because stress is known to impair the efficacy of extinction training, we hypothesized that social buffering during the extinction training in turn enhances the efficacy of extinction training. On day 1, the subjects received 7 repetitions of a 3-sec auditory CS (8kHz, 70dB) that terminated concurrently with a 0.5-sec foot shock (0.55mA) in the conditioning box (context A). On day 2, the subjects in the Alone and Social situation underwent the extinction training without or with a non-conditioned associate, respectively, in the extinction box (context B) in which the subjects received 24 CS presentations with random intervals varying from 1 to 2-min (Training group). We also prepared the Non-training groups in both situations by keeping the subjects during the same period in the extinction box without any CS presentation. On day 3, the efficacy of extinction training was evaluated by observing the intensity of freezing during the 20-sec after the onset of 2 CS in the extinction box (context B). In the Alone situation, the Training group showed an equivalent intensity of freezing with the Non-training group. In contrast, the Training group showed a decreased intensity of freezing as compared to the Non-training group in the Social situation. These results suggest that the insufficient extinction training came to suppress freezing when an associate was present during the extinction training. We also observed in the Social situation that the Training group showed the similar intensity of freezing with the Non-training group when we tested in a box (context C) that was different from the extinction box, suggesting that the effects of social buffering was context specific. Taken together, these results suggest that social buffering enhances the efficacy of extinction training.

10. **Establishing a role for cortico-thalamic circuitry in cue-driven behaviors.** Joshua L. Haight[1], Kurt M. Fraser[1], Huda Akil[1], Susan M. Ferguson[2], and Shelly B. Flagel[1]. [1]University of Michigan, [2]University of Washington. Recently evidence has emerged suggesting the paraventricular nucleus of the thalamus (PVT) is a critical component of the neural circuitry underlying the processing of reward-associated cues, but much of this previous work is confounded by the fact that Pavlovian conditioned reward cues can act as both predictive and incentive stimuli. Here we used a unique animal model to parse the incentive from the predictive properties of reward cues. When rats are exposed to a Pavlovian conditioning paradigm, wherein a discrete cue predicts food reward, two distinct conditioned responses emerge. Some rats, termed sign-trackers (STs), attribute incentive salience to the cue. For others, termed goal-trackers (GTs), the cue serves as a predictive stimulus. We investigated the role of the PVT in the expression and acquisition of these conditioned responses (CRs). First outbred rats were trained in a Pavlovian conditioning task. Following training, ibotenic acid was used to lesion the PVT and the expression of sign- and goal-tracking CRs was measured. When compared to sham controls, PVT lesions attenuated the expression of a goal-tracking response, and increased a sign-tracking response selectively in GTs. Second, we assessed the effects of PVT lesions on the acquisition of sign-and goal-tracking CRs, using selectively bred rats in which it is known a priori whether these rats will acquire a sign- or goal-tracking CR. PVT lesions

were performed prior to training and following recovery rats underwent 12 sessions of Pavlovian conditioning. STs with PVT lesions showed an exaggerated sign-tracking response, compared to sham controls of the same phenotype. In addition, PVT lesions attenuated the development of a goal-tracking response in rats with an inherent tendency to goal-track. We are currently following up these studies using more sophisticated techniques to explore which aspects of PVT circuitry are involved in sign- and goal-tracking behaviors. These methods include retrograde tracing from the PVT combined with c-fos immunohistochemistry, as well a novel FLEX-DREADD (Designer Receptors Exclusively Activated by Designer Drugs) technique. These experiments will allow us to parse the role of specific afferent projections to the PVT in the expression of sign- and goal-tracking behaviors. Preliminary results suggest that prelimbic cortical afferents to the PVT are involved in mediating both sign- and goal-tracking behaviors and that "top-down" communication from the prelimbic cortex to the PVT plays a critical role in the attribution of incentive motivational properties to reward cues. Funding Acknowledgments: NIDA F31 DA037680-01A1 (JLH); NIDA T32 DA007821 (JLH).

11. **Differential effects of Resveratrol on the expression of BDNF transcripts and protein in the hippocampi from adult and embryonic rat brain.** Shahla Shojaei[1], Mohammad Reza Panjehshahin[1], Sayed Mohammad Shafiee[1], Zahra Khoshdel[1], Mohammad Borji[1], Ghasem Ghasempour[1] and Ali Akbar Owji1*. [1]*Author for correspondence: Ali Akbar Owji, E mail: owjiaa@sums.ac.ir, Research Center for Psychiatry and Behavioral Sciences, Shiraz University of Medical Sciences, Shiraz, Iran. Background: Induction of brain-derived neurotrophic factor (BDNF) expression in the hippocampus has shown to play a role in the beneficial effects of the phytoestrogen, resveratrol (RSV), on the learning and memory. The BDNF gene has a complicated structure with nine 5' noncoding exons (I-IXa), each of which can splice to a common coding exon (IX) to form a functional transcript. Estrogens increase levels of BDNF transcripts in the hippocampus of rats. The aim of this study was to assess the effects of oral RSV on the splicing pattern of BDNF transcript in the hippocampi of rats. Methods: RSV (60 or 120 mg/kg BW) was administered orally to pregnant rats from days 1 to 20 of gestation. Hippocampi of adults and embryos were dissected 24h after the last administration of RSV. Extracts from hippocampi were subject to quantitative (q) RT- PCR and Western blotting respectively to assess splicing pattern of the BDNF transcripts and levels of pro-BDNF protein. Results: RSV (120 mg/kg BW) caused a statistically significant increase in the expression levels of BDNF exons III, IV and IX but not the exon I in the hippocampi of adult rats(Kruskal-Wallis test/Mann-Whitney U test with Bonferroni correction, $P \leq 0.05$). Levels of pro-BDNF protein remained unchanged in the hippocampal tissues from both adult and embryonic rats treated by RSV (60 or 120 mg/kg BW). Conclusion: Our results show that RSV differentially activates promoters of the BDNF gene in the hippocampus of pregnant rats.

12. **Vaginal and uterine absorption of estradiol from male seminal emissions during mating in mice.** Tyler Pollock, Denys deCatanzaro. McMaster University. The potent estrogen, 17β-estradiol (E_2), has previously been found to transfer from male excretions to female blood circulation during 48-72 h of cohabitation. Such transfer between conspecifics has been observed in both mice and bats. It is facilitated by the low molecular mass and lipophilic nature of unconjugated E_2, which allows absorption via nasal and percutaneous routes and arrival the female's uterus and brain where it may have pheromonal effects. In new experiments, we traced small quantities of tritiated estradiol (^{3}H-E_2) administered to male mice. Substantial radioactivity was evident in the testes, epididymides, preputials, and vesicular-coagulating glands of males directly given doses of ^{3}H-E_2 equivalent to a small fraction of their endogenous E_2. When such males were paired with ovariectomized females made sexually receptive by E_2 priming and progesterone injections, radioactivity began to be evident in the females' circulation and organs within minutes of the commencement of sexual mounting, and it

progressively increased in correlation with the number of intromissions. Whenever a male ejaculated, radioactivity spiked in the female's uterus to levels greatly exceeding those observed during intromissions, and it progressively entered her blood and was observed in diverse organs including her brain. Indeed, the male copulatory plug that is observed in this species contained radioactivity at levels comparable to those of the male's tissues. When deposited in the female's reproductive tract at ejaculation, this plug provided a repository of E_2 that released this steroid into the female's system for at least 18 h. There is very dense concentration of estrogen receptors in the mammalian female reproductive tract and also in the ventromedial hypothalamus. Direct receipt into the uterus can allow E_2 to influence estrogen receptors without being subjected to enzymes in the liver and elsewhere. Transfer of E_2 during mounting is potentially relevant to male's induction of regular female estrous cycling in the Whitten effect. Uterine repositories of E_2 following ejaculation could induce LH surges, ovulation, progesterone release, and preparation of the uterus for ovo-implantation. *Funded by grants from the Natural Sciences and Engineering Research Council of Canada to D. deCatanzaro.*

13. **A novel task to assess reversal learning in mice in a home-cage environment.** E. Remmelink[1,2,3], M. Verhage[2], A.B. Smit[3], M. Loos[1], *[1]Sylics (Synaptologics B.V.), Amsterdam*. *[2]Department of Functional Genomics, CNCR, VU University, Amsterdam*. *[3]Department of Molecular and Cellular Neurobiology, CNCR, VU University, Amsterdam.* Several neurological and psychiatric disorders are characterized by deficits in cognitive flexibility. Measuring cognitive flexibility in mice enables the investigation of mechanisms underlying these deficits. The majority of currently available behavioral tests targeting this cognitive domain are operant tasks, which require food-deprivation and extended training periods. Here, we describe a novel test for measuring reversal learning in an automated home-cage environment (PhenoTyperTM) that circumvents extended training periods and food-restriction and reduces labor intensive and stress-inducing animal-handling. All behavior was video tracked and hardware actions were triggered by the position of the mouse. After an initial habituation period to the home-cage, a wall with three holes was placed in front of the pellet dispenser spout. For two days, mice had to learn to earn all their food by going through the left hole in the wall (Initial learning). During the subsequent 2 days, the correct and rewarded hole was switched to the right hole (Reversal learning). During this task the dispenser distributed 1 reward for every 5 times the mouse went through the correct hole (FR5 schedule). The number of passages needed to reach a criterion of 24 out of 30 entries through the correct hole, computed as a moving window, was used as a measure of performance during both stages. Perseverative as well as random errors were assessed during the reversal learning stage. The total number of entries through the wall, and the distance moved, were assessed as measures of general activity. Most mice tested were able to attain the performance criterion of 80% correct within 1 day. As expected, mice took significantly longer to attain this performance criterion during the reversal phase. All individuals were able to attain the criterion within the two available reversal learning days. Task activity was predominantly limited to the dark phase, suggesting that task performance had no impact on circadian rhythm. Additionally, we tested mutant mice with known deficits in either initial learning or reversal learning, and were able to replicate those deficits by using our task. To conclude, we have developed a short 4-day protocol for reversal learning, which runs without human intervention. This task provides an efficient way of screening mice for discrimination and reversal learning in a home-cage environment, in which handling is absent and no food-restriction is required.

14. **Emotional aspects of event learning in rats: Characterization and neural basis.** Jorge R. Bergado-Acosta[1], Marcel Brosch[1,2], Johann Bruning[1], Milad Mohammadi[1,2], Taygun Uzuneser[1,2], Markus Fendt[1,3. 1]Institute for Pharmacology and Toxicology; [2]Integrative Neuroscience Program; [3]Center for Behavioral Brain Sciences, University of Magdeburg, Germany. Dangerous events can be

better coped if there was some learning from previous dangerous events. Important to learn is: What caused the event? What stopped it? What was not associated with it? During such event learning, environmental cues which preceded the dangerous event are associated with the emotion “fear” and induce fear behavior in future. Thereby, the learning of such cues can help to avoid dangerous events in future, or to handle them more efficient. The second class of environmental cues which were present after the offset of a dangerous event or in the absence of the dangerous event are associated with the emotion “relief” or "safety". Such cues can induce appetitive behavior in future and can help to avoid or to stop dangerous events in future and/or to encounter such event with less fear. Thus, event learning consists of different learning phenomena with very different emotional and behavior consequences: fear learning, safety learning and relief learning. Since fear learning is already well investigated, our research is focused on relief and safety learning. Recent data from our laboratory showed that the nucleus accumbens is crucial for relief learning but not safety learning. On a behavioral level, conditioned safety but not conditioned relief is context-dependent. Recent studies demonstrated that the acquisition of conditioned relief is mediated by NMDA and dopamine D1 and D2 receptors within the nucleus accumbens and protein synthesis dependent. We think that understanding relief and safety learning will also improve our understanding of the learned emotional, motivational and behavioral consequences of aversive events, in particular the appetitive or rewarding ones which were neglected so far. This may help to explain pathological behavior after traumatic events (e.g. post-traumatic stress disorder).

15. **Behavioral and Hormonal changes in male and female rats due maternal separation during breastfeeding.** Dueñas Z[1*], Riveros-Barrera I[1], Caicedo-Mera CJ[1] and Martín L. 1 Facultad de Medicina, Universidad Nacional de Colombia. Long lasting negative effects due early stress like maternal separation during breastfeeding (MSDB) has being reported in different animal models including rats. Some of those effects are related with changes in stress response, anxiety and motor exploration; however most of the reported data are in males and few compare both male and females. In this work our aim was to identify if MSDB modifies motor exploration and object recognition memory and to measure the basal levels of corticosterone, adenocorticotropine, oxytocin and vasopressin hormones, comparing males and females. Wistar rats were habituated to reversed light-dark cycle with water and food *ad libitum*. After pregnancy, each mother was kept in one cage and the delivery day was a day 0. After postnatal day 1 the pups were separated from their mother until day 21(breastfeeding period), in two intervals of 180 minutes: 6:30 to 9:30 and 14:00 to 17:00. Another group was undisturbed and used as a control group. After postnatal day 21 rats were separated by sex and treatment. At 35/40 day spontaneous motor activity was evaluated through open field test, measuring frequency and duration of central and peripheral quadrant crossing. In addition, rearing and corner exploration behaviors were quantified. The following day, object recognition memory test was applied and subjects were sacrificed in order to take blood samples for the hormones measurements and brain and other organs for other analysis. Our data shows that separate females group expressed anxiety and hypo activity behaviors while separate males group presented anxiolytic and hyperactivity behaviors. Both separate groups exhibited lower exploration time of new objects in memory test. Related with hormone measurements, we found that corticosterone and ACTH levels in both groups control and separated were higher in males and females, but oxytocin decrease in separated females and increase in separated males and finally the vasopressin levels decrease in both separated groups males and females. Taken together, these results allow us to suggest that neuroendocrine responses associated to Hypothalamic-Pituitary-Adrenal axis stress regulation could mediate behavioral expressions in a sex-dependent way, which probably involve interactions with sexual hormones such as ovaric steroids. Funding acknowledgements: Universidad Nacional de Colombia. DIB-FACMED. Grant Number 14800.

16. **Individual differences in human susceptibility to alpha-band EEG 'entrainment' induced by photic stimulation**. Cocchieri, C., Thalheimer, W., Ashman, J., Storrs, T., Foster, V., Devik, E., Langford, W., Saia, D., Flores, J., Flores, M., Danbury, M., Cetrulo, G., and Rossi III, J. Florida Gulf Coast University, Ft. Myers, FL. Since Hans Berger first reported his discovery of the "*Elektrenkephalogramm",* and the 10hz synchronous rhythm in human EEG that evolves during sustained eye closure and relaxation, the relationship between relaxation and the "Berger rhythm" has been extensively studied. Written comments about the sensations of relaxation and tranquility induced by watching flickering light, such as that produced by a sparking fire, date back to the ancient Greeks. However, it wasn't until 1934 that Adrian and Matthews, demonstrated that exposure to light flickering at frequencies of 8, 10, 12 and 18hz could synchronously evoke EEG responding at those frequencies. In the ensuing years, significant interest has developed in the applications of entraining EEG to frequencies of light flashes and/or sound pulses which may be physiologically beneficial, although many of the developed therapeutic protocols do not include EEG verification of the entrainment. Empirically, most research effort has been directed at entrainment frequencies within the alpha-band (7-13hz), but a common shortcoming of most evaluative work has been the pre-selection of specific frequencies, usually 8, 10, or 12hz, and the treatment of all participants with just one of those frequencies. The current study evaluated the susceptibility of 14 participants, age 20 - 60, to 12 white light flicker entrainment frequencies from 7.0Hz to 12.5Hz presented in 0.5Hz increments using a commercially available 'goggle-type' Audio/Visual Stimulator (AVS). Each participant received the identical skipped-order frequency presentation wherein a 5 min period of pink noise preceded a 5 min entrainment period which was followed by 5 min of pink noise. EEG was recorded from an electrode just superior to the external occipital protuberance throughout each presentation series. The results suggest that substantial individual sensitivity differences exist among the participants with regard to the specific frequencies to which they would entrain and the overall degree of entrainment achieved. These effects were found to be independent of age and gender of the participants.

17. **Are standard laboratory animals more stress-sensitive?** ArchanaAshokan[1] and RupshiMitra[1]. School of Biological Sciences, Nanyang Technological University. [1] School of Biological Sciences, Nanyang Technological University, Singapore 637551. Animals raised in a laboratory devoid of natural settings present a number of physiological and behavioral changes contrasting their wild counterparts. While wild animals have strong yet stable emotional responses that are accompanied by enhanced active coping strategies, laboratory animals exhibit more avoidance indicating passive coping against stressors. The former demonstrate more aggressiveness. These differences in the physiology and behavior could conceivably be attributed to the psychological stress imparted by a lack of natural habitat settings. Exposure to environmental enrichment (EE) provides a complex setting, which emulates the wild approximately. EE is filled with exploratory, social, emotional, and motor stimulations for the animals. The purpose of this study is to compare the stress-responsive behavior and underlying brain mechanism between animals housed in standard laboratory conditions and in EE. This study suggests that animals housed in EE show accelerated habituation to a novel environment as compared to their control counterparts housed in standard laboratory cages. Furthermore, the latter present greater tendencies towards depressive-like symptoms. EE also brings about striking changes in the neuronal structures of the hippocampus associated with habituation and depressive behaviors. In conclusion, this study reassesses the utility and reliability of standard control animals in the context of stress-related behavior.

18. **Enriched environment: A resilience-inducer involving BDNF modulation.** Akshaya Hegde[1] and Rupshi Mitra[1.] School of Biological Sciences, Nanyang Technological University. [1] School of Biological Sciences, Nanyang Technological University, Singapore 637551. The neurons in a mammalian brain exhibit neuronal plasticity in response to various environmental stimuli, including stress. One of the crucial factors which drive these alterations is brain-derived neurotrophic factor (BDNF). BDNF is known to play a cardinal role in driving intracellular signaling pathways for neuronal survival, morphogenesis, and plasticity in the brain. It is also associated with stress-induced pathophysiologies. The hippocampus, the medial prefrontal cortex (mPFC), and the basolateral amygdala (BLA) are the three primary regions involved in the regulation of stress physiology which also shows a differential regulation in BDNF mRNA as a response to chronic stress. The current study focuses on comparing the mRNA abundance of BDNF in these three different regions, between male rats exposed to short-term enrichment (14 days) and their control counterparts, both in the presence and absence of chronic stress. Chronic stress was induced by immobilizing the rats consecutively for 10 days (2 hours/day). The three primary stress-responsive regions (BLA, hippocampus, and mPFC) were analyzed for BDNF mRNA abundance using qPCR. In BLA, it was observed that chronic stress increased BDNF mRNA abundance while EE reversed this effect. This region especially corresponds to hyperactivity under chronic stress, in turn leading to manifestations of anxiety. EE presented similar effects in the hippocampus as observed in the BLA. This region plays a crucial role for processing working-memory. In contrast to both areas, mPFC showed no change in BDNF mRNA expression in response to stress or EE. The findings in both hippocampus and BLA are critical in order to further probe the cellular underpinnings of memory and anxiety respectively. Moreover, this forms a basis for potential therapeutic strategies to counter stress-disorders by modulating BDNF through environmental manipulation.

19. **Involvement of orexin in the sex-specific effect of relaxin-3 on food intake in rats.** Calvez, Juliane ; Lenglos, Christophe ; De Avila, Camila ; Timofeeva, Elena. CRIUCPQ, Faculty of Medicine, Department of Psychiatry and Neuroscience, Laval University. BACKGROUND: Relaxin-3 (RLN3) is a neuropeptide thought to modulate food intake, stress and arousal. We have recently shown that the orexigenic effect of RLN3 was stronger in female rats. This effect might be in part due to higher activation of the anorectic corticotropin-releasing factor in the paraventricular nucleus of the hypothalamus (PVN) in male rats. The goal of this study was to determine whether other hypothalamic regions and neuropeptides are potentially involved in the sex-specific orexigenic effect of RLN3. METHODS: 800pmol of RLN3 or vehicle was injected into the lateral ventricle of female and male rats. Food intake was measured after a first intracerebroventricular (icv) injection and rats were euthanized after a second icv injection to determine mRNA expression of the marker of neuronal activity *c-fos* in hypothalamic nuclei by *in situ* hybridization. According to the c-*fos* results, vasopressin and oxytocin mRNA expression was evaluated in the PVN as well as orexin and melanin-concentrating hormone (MCH) in the lateral hypothalamus (LH). RESULTS: As previously shown, 2-h food intake was increased after RLN3 icv injection and the increase was significantly higher in female than male rats. No effect of RLN3 injection was found on *c-fos* mRNA expression in the arcuate nucleus, the dorsomedial hypothalamic nuclei or the ventromedial hypothalamus. Increased c-*fos* mRNA expression was observed in the PVN and accordingly, we showed an increased mRNA expression of vasopressin in the parvocellular part of the PVN in RLN3 injected-male rats and an increased of mRNA expression of oxytocin in the magnocellular part of the PVN in male and female RLN3-injected rats. Furthermore, c-*fos* mRNA expression was higher in female RLN3 rats in the LH. While MCH mRNA expression in the LH was not affected by RLN3 icv administration in either of the genders, orexin mRNA expression was significantly increased in female rats in the lateral region of the LH. CONCLUSION: Our results suggest that an alteration in the

anorectic oxytocin signalling is unlikely to be involved in the orexigenic effect of RLN3 but that the LH and especially the orexin neuronal population may contribute to the differential effect of RLN3 on food intake in male and female rats. The ability of orexin to increase food intake may occur through its stimulation of arousal as well as an increase in motivation which is consistent with the behavioural effects of RLN3 that have been previously demonstrated.

20. **Prolonged maternal separation affect corticosterone levels and social play behavior in adolescent male but not female Wistar rats.** Stina Lundberg[1], My Martinsson[1], Ingrid Nylander[1], Erika Roman[1]. Early-life experiences are an important factor influencing further development of the individual. Adverse experiences leads to exposure of early stress that can have detrimental effects on several physiological systems. Maternal separation (MS) is a rodent model used to study the effects of early-life experiences. In this study two separation conditions were used: daily 15- (MS15) and 360-minute (MS360) separation of the litter from the dam during the first three postnatal weeks. In early adolescence, male and female offspring were subjected to a stress reactivity test for analysis of corticosterone levels prior to and after stress. In addition, social play behavior was assessed during mid-adolescence. There was a clear difference between male and female offspring in both tests performed. In the stress reactivity test there was no difference between the female groups while MS360 males showed higher basal corticosterone level than the MS15 males and a smaller decrease in corticosterone in the recovery phase. The amount of pinning during social play was affected by rearing with MS360 males having a higher frequency than MS15 males, while there was no difference among the females. That males but not females are affected by prolonged MS have previously been shown in adult animals and here we show that the same is true for adolescent animals. Altered corticosterone levels during adolescence might in adulthood lead to changes in stress reactivity; what impact the slight change in social play might have needs further investigation. [1]Neuropharmacology, Addiction and Behavior, Department of Pharmaceutical Biosciences, Uppsala University, Sweden. Funding support: Alcohol Research Council of the Swedish Alcohol Retail Monopoly, and the Swedish Research Council (K2012-61X-22090-01-3).

21. **Control of the septohippocampal pathway and learning and memory by relaxin-3/RXFP3 neural networks: Viral-based studies in transgenic mice.** Haidar M[1,2], Hawkes D[1], Guèvremont G[3], Olucha-Bordonau FE[1,4], Ma S[1,2], Bathgate RAD[1,2], Timofeeva E[3], Smith CM[1,2], Gundlach AL[1,2] [1]The Florey Institute of Neuroscience and Mental Health, [2]Florey Department of Neuroscience and Mental Health, The University of Melbourne, Victoria, Australia, [3]Department of Psychiatry and Neurosciences, Faculty of Medicine, University of Laval, Quebec, Canada, [4]Department of Medicine, Universitat Jaume I, Castellon de la Plana, Spain. The 'septohippocampal system' (SHS) is regulated by GABA projection neurons of the brainstem 'nucleus incertus' (NI), including a population that expresses relaxin-3 peptide, which interacts with specific receptors (RXFP3) on neurons in medial septum (MS), hippocampus and other SHS nodes. Local RXFP3 modulation in the MS alters hippocampal ('theta rhythm') activity and spatial memory in rats; via putative actions on GABA and ACh septohippocampal-projection neurons, but similar studies in mice have not been conducted and the nature of RXFP3 effects within the MS/hippocampus are not known. Thus, we are studying relaxin-3/RXFP3 systems in the SHS of relevant transgenic mice. Initial studies of the neurochemical phenotype of topographically distributed RXFP3-positive neurons in the hippocampus in RXFP3-Cre/YFP 'reporter' mice revealed putative RXFP3-related YFP staining within calretinin-positive neurons in the ventral dentate gyrus hilar region. Secondly, using Cre/LoxP recombination methods, we assessed affective behaviour and working memory in mice with targeted deletion of RXFP3 from the dentate gyrus. In an initial cohort, 'floxed-RXFP3' mice injected bilaterally in the dorsal hippocampal hilar layer with Cre recombinase-expressing adeno-associated virus (AAV1/2-

Cre/eGFP) displayed similar locomotor activity, anxiety-like behaviour (light/dark box and elevated plus maze tests), and short-term working memory (Y-maze) to AAV1/2-eGFP-injected control mice (n=8/5, p>0.05). In contrast, this treatment enhanced long-term spatial memory in the Morris water maze, reflected by increased time in the target quadrant during the probe trial; n=8,5 $p<0.05$, unpaired t-test), with no differences in spatial learning detected during acquisition trials (n=8/5, $p>0.05$). The persistence of RXFP3-deleted mice in the target zone may relate to lower behavioural flexibility, whereby mice persist with an 'incorrect solution' rather than modifying their behaviour. Using *in situ* hybridization histochemistry, we are now assessing the overlap of RXFP3 mRNA expression and YFP staining, and changes in RXFP3 mRNA levels in the hippocampi of AAV1/2-Cre/eGFP injected and control mice, as an index of receptor deletion. Further studies are underway to extend these findings, but current data are consistent with the possible regulation of learning and memory retrieval by hilar GABA interneurons and calretinin-positive hilar mossy cells and possible RXFP3 modulation of these networks.

22. **Most people use both allocentric and egocentric strategies to solve a dual-strategy virtual Morris water maze.** Thomas Ferguson[1], Dustin van Gerven[1], Ronald Skelton[1]. [1]University of Victoria, Victoria, BC, Canada. Men are often thought to be better at navigating allocentrically, using cognitive maps and their hippocampus, whereas women are thought to prefer to navigate egocentrically, using routes built from stimulus-response associations by their caudate nucleus. Research on the neural basis of spatial navigation has tended to focus on one strategy or the other. A common assumption seems to be that these navigational strategies are mutually exclusive, either within circumstances or within individuals. However, in one of the few studies to examine both strategies at the same time, rats were found to turn their heads towards allocentric landmarks at the start of the trial, and egocentric landmarks at the end (Whishaw and Mittleman, 1986). In the present study we tested 31 male and 31 female undergraduates in a dual-strategy virtual Morris water maze. This maze could be solved by going to a place in the arena relative to a 360^{o} virtual landscape or to 1 of 8 coloured spheres floating at about head level in the arena. After each of 10 learning trials, participants were asked to show us where they thought the platform was. On these strategy probe trials, the cue-sphere was swapped to the opposite quadrant. On these probes, 73% of participants went to the quadrant with the cue-sphere (an egocentric strategy), 26% went to the correct place in the arena (an allocentric strategy) and only 1 person never learned the platform location. When forced to use an allocentric strategy on a separate probe trial without spheres, most participants (66%) were able to choose the correct quadrant using only the landscape, regardless of their preferred strategy on previous trials. When forced to use an egocentric strategy on a probe trial that included the 8 spheres but occluded the landscape, all but 4 participants (94%) chose a location very near either the cue sphere or the sphere in the opposite quadrant (i.e., over the allocentrically correct place). Males and females did not differ in strategy choice or performance. When tested for their ability to use an allocentric strategy (in a virtual Morris maze with no spheres) all previously allocentric navigators and 88% of previously egocentric navigators had learned the correct quadrant by the 10th trial. These data indicate that neither men nor women are bound by a single navigational strategy but rather, both have the cognitive capacity to use allocentric and egocentric strategies, alone or in conjunction, as the circumstances require.

23. **Signaling by tuberoinfundibular peptide of 39 residues in the medial amygdala modulates remote fear memory.** Mumeko C. Tsuda, Ted B. Usdin. Section on Fundamental Neuroscience, NIMH, NIH, Bethesda, MD. Fear-related psychopathologies such as post-traumatic stress disorder are characterized by impaired fear memory extinction. Our recent neuroanatomical and behavioral findings suggest that the neuropeptide tuberoinfundibular peptide of 39 residues (TIP39), via its

receptor, the parathyroid hormone 2 receptor (PTH2R), modulates fear memory (Coutellier and Usdin, Behavioural Brain Res, 2011). We are now investigating the anatomical and cellular localization of TIP39's contribution to enhanced fear memory. PTH2R knockout (PTH2R-KO) and wild-type (WT) male mice were exposed to a single 2 second 1.5 mA foot shock and fear-recall was assessed as conditioned freezing during re-exposure to the shock context after 28 days. Compared to WT, PTH2R-KO mice had increased freezing in the shock context, suggesting enhanced fear-recall in mice lacking TIP39 signaling. The medial amygdala (MeA), which contains a high density of PTH2Rs and TIP39 containing terminals, projects to the basolateral and central amygdala, areas that have well established roles in fear memory. To evaluate whether TIP39 signaling in the MeA modulates fear memory, we stereotaxically injected viruses encoding a secreted PTH2R antagonist (HYWH) + GFP or GFP only (control) into the MeA of WT male mice. Mice then received a single foot shock as described above and fear recall was evaluated 28 days later. Similar to PTH2R-KO, mice with HYWH MeA injection had greater freezing than controls. We then used the designer receptor exclusively activated by designer drug (DREADD) pharmacogenetic technique to examine whether signaling through cells that TIP39 acts on in the MeA is required during initial coding and/or recall of fear memory. A Cre-dependent Gi-coupled DREADD virus that can suppress neuronal activity was injected into the MeA of mice with PTH2R driven Cre expression. Saline or clozapine-N-oxide (CNO), a DREADD agonist that has no effect on endogenous receptors, was administered (1) 1 hour before foot shock or (2) 1 hour before fear recall testing. Fear recall was evaluated 28 days after foot shock. Inhibiting PTH2R expressing neurons with CNO at the time of foot shock increased freezing during fear recall, but inhibition at the time of recall had no effect, compared to saline treated mice. Taken together, these findings demonstrate that TIP39 signaling within the MeA at the time of aversive event contributes to modulation of long-term fear recall of traumatic experience.

24. **Regulation of discriminative fear conditioning by prefrontal and striatal subregions.** Patrick T. Piantadosi[1], Dylan C.M. Yeates[1], Stan B. Floresco[1]. University of British Columbia. Fear is a highly salient emotion that can control motivated behavior. The neural substrates underlying such behavior have been investigated using Pavlovian fear conditioning, whereby an organism is exposed to a single conditioned stimulus (CS) that becomes predictive of an aversive unconditioned stimulus. Less is known about the circuitry underlying appropriate fear discrimination in the presence of both an aversive conditioned stimulus (CS+) and one that is explicitly neutral (CS-). Here, we used reversible inactivations to examine the contribution of two subregions of the rat medial PFC (mPFC), the prelimbic (PL) and infralimbic (IL) cortex, and two subregions of the nucleus accumbens, the shell (NAcS) and core (NAcC), to the acquisition and expression of discriminative fear conditioning. Male Long Evans rats were trained to lever press for sucrose reward on a variable-interval 60s (VI-60) reinforcement schedule. They were then subjected to discriminative fear conditioning entailing eight, 30s presentations each of a CS+ (9kHz tone and continuous cue light terminating with 0.5mA/0.5s footshock) and a CS- (1kHz tone and flashing house light, no shock). Two days later, rats underwent a test session during which each CS was presented four times during VI-60 lever pressing. A second test session was given on the following day, to examine potential extinction learning during test. To assess the impact of aversive conditioning on motivated behavior, the suppression of lever pressing during each CS served as the index of conditioned fear. Rats received inactivation of either the IL or PL (75ng baclofen/muscimol in 0.33µl saline per side) or NAcS or NAcC (75ng baclofen/muscimol in 0.3µl saline per side) or saline infusion prior to either the conditioning or test phase of the task. Control rats in each condition displayed appropriate discrimination, suppressing lever pressing during the CS+ exclusively. Inactivation prior to conditioning had no affect on the subsequent expression of discriminative fear during the first test day, regardless of the region inactivated. However, IL inactivation prior to conditioning lead to somewhat more rapid extinction of fear on the second test

day. Interestingly, inactivation of PL, IL, and NAcS prior to the expression test markedly reduced suppression in response to CS+ presentations, suggesting that these regions contribute to motivational suppression in a fear context. Inactivation of NAcC, however, had no impact on conditioned suppression. These results point to a potential corticostriatal circuit regulating the ability of aversive cues to control ongoing motivated behavior.

25. **Role of striatal cholinergic interneurons in set-shifting in the rat.** Sho Aoki, Andrew W. Liu, Aya Zucca, Stefano Zucca, and Jeffery R. Wickens. Okinawa Institute of Science and Technology, Japan. The ability to change strategies in different contexts is a form of behavioral flexibility. The striatum has been shown to contribute to certain forms of behavioral flexibility such as reversal learning. We here report on the contribution of striatal cholinergic interneurons – a key element in the neuronal circuit of the striatum – to strategy set-shifting in which an attentional shift from one stimulus dimension to another is required. We made lesions of rat cholinergic interneurons in dorsomedial or ventral striatum using a specific immunotoxin and investigated the effects on set-shifting paradigms using different operant procedures, and on reversal learning. The present set-shifting tasks characterized by three different operant conditions required animals to initially learn a response strategy to obtain a reward (for example, always press a right lever), in which a visual cue was either Condition 1) not presented, 2) was always above the correct lever or 3) was randomly presented above one of left or right levers. During the shift, animals were required to learn a visual cue strategy where they had to follow a lever on which a light cue was illuminated. Lesioned animals were unimpaired on learning of an initial response strategy across all the three conditions. However, when shifting a strategy that required attention to a novel visual cue (Condition 1), rats with lesions of cholinergic interneurons in ventral striatum showed a significant impairment: an increase in the number of perseverative errors. When shifting a response to a visual cue that was previously relevant (Condition 2), neither lesions affected. When switching a strategy by attending to a previously irrelevant visual cue (Condition 3), cholinergic interneuronal lesions of the dorsomedial striatum resulted in an increase of perseverative errors. In this condition, the number of never-reinforced errors was significantly decreased in both dorsomedial and ventral lesion groups. Reversal learning was not affected by either lesion. These results suggest that cholinergic interneurons of dorsomedial and ventral striatum contribute to inhibiting the use of a now invalid response strategy during a shift, but they play the role in different contexts in each when a previously irrelevant or novel stimulus becomes relevant for shifting behavioral strategies. This study was supported by Human Frontier Science Program and the Sasakawa Scientific Research Grant from the Japan Science Society.

26. **Sex differences in the acquisition of conditioned disgust behaviour in the rat.** Cloutier-Duke, Caylen J[1]; Kavaliers, Martin[1]; Ossenkopp, Klaus-Peter[1]. [1]Western University Canada (London, Ontario). Anticipatory Nausea and Vomiting (AN/V) is a classically conditioned behaviour observed among a significant proportion of cancer patients undergoing chemotherapy. The pairing of a nausea-inducing cytotoxic drug treatment (US) with the hospital context (CS) leads to nausea and/or vomiting upon re-exposure to the hospital context (CR), prior to any subsequent chemotherapy treatment. This form of conditioning is robust, and many choose to forego further treatment that could be life-saving. Within the subset of patients who experience AN/V, evidence suggests that there is a higher incidence in females. The present experiment examined sex differences in the establishment of classically conditioned disgust reactions (i.e., conditioned gaping behaviour) in the rodent model of Anticipatory Nausea. Rats lack an emetic reflex, but display a conditioned gaping behaviour that is topographically similar to the pre-vomiting oral response (i.e., retching) in the shrew. Thus, conditioned gaping responses present as a reliable index of nausea in the rat. On each of 4 days (72 h apart), 39 naïve adult male and female Long-Evans rats (19 male, 20 female) were administered an

intraperitoneal injection of either 128 mg/kg lithium chloride (LiCl; 0.15M, 20 ml/kg) or a control injection of 0.9% isotonic saline (NaCl; 20 ml/kg), immediately prior to exposure to a novel context (opaque white Plexiglas chamber) for 30 minutes. 72 h following the last conditioning day, each animal was re-exposed to the conditioning context for 10 minutes on a Drug-free Test Day, where conditioned aversive behaviours (e.g., gaping, paw treading, forelimb flails, chin rubs) and spontaneous orofacial behaviours (e.g., mouth movements, tongue protrusions) were recorded. Consistent with previous findings, significantly higher frequencies of conditioned aversive behaviours were observed in LiCl-treated rats, relative to saline controls, in both males and females. Furthermore, females displayed significantly higher frequencies of conditioned gaping behaviour specifically, relative to males, demonstrating a robust sex difference in the establishment of conditioned disgust reactions (i.e., Anticipatory Nausea) in the rat across all parts of the estrous cycle. The current findings are consistent with evidence of a sex difference in the human population, and provide a preclinical model for testing sex differences in the efficacy of anti-emetic drugs, which also function to reduce nausea.

27. **Discovering macroscopic networks and their modulation in animal models of repetitive disorders.** Winter, Christine. Repetitive behaviors constitute isolated phenomena often preceded by so-called premonitory urges that are alleviated by the action of the repetitive action. Though incompletely understood, they are believed to be caused by disruptions within the basal ganglia-thalamo-cortical (BGTC) circuit and the dopamine system. Traditional treatment approaches are often associated with poor symptom alleviation, treatment resistance and side effects severe enough to require discontinuation of the treatment. To develop rationale driven therapeutic interventions the spatial and temporal disruption of the macroscopic function of distributed brain networks needs to be considered. We will here present an approach that uses different animal models of repetitive behavior in parallel to untangle the temporo-spatial disruption of the BGTC circuit and the dopamine system in the generation of repetitive behavior, i.e. the quinpirole rat model of compulsive behavior, the dopamine transporter overexpressing rat model of Tourette-Syndrome and the maternal immune activation rat model of schizophrenia. We will show how we test therapeutic interventions that directly target the origins of the distinct symptoms based on a thorough description of brain activity and biochemical abnormalities across the pathology models. Given its unique ability to target specific brain regions, we will show how deep brain stimulation (DBS) can be used to substantiate the pathophysiological and therapeutic relevance of BGTC circuit compartments. We will propose advancements to conventional DBS that also considers the temporal disruption of the macroscopic function of the BGTC circuits in the manifestation of repetitive behaviors. We will conclude that studies are mandatory that correlate neurotransmission or oscillatory activity and symptom presentation in order to provide the rationale for the development of feedback controlled treatment approaches capable of closed-loop intervention responsive to the targeted symptoms.

28. **Social Factors Modulate Toxin-Induced Disgust Responses in Rats.** Boulet, Nathalie; Kavaliers, Martin; Ossenkopp, Peter; Cloutier, Caylen. University of Western Ontario. Disgust responses are observed across numerous species and are considered to have their origins in defenses against toxicity and pathogens. Disgust encompasses a range of behavioral responses including those associated with vomiting or emesis. Non-emetic species, such as the rodent, lack the musculature and brainstem pathway needed to expel harmful toxins. Instead, rats display distinctive disgust reactions when given a substance previously paired with sickness. Of these disgust reactions, the gaping reaction is the most reliable. Results of comparative, evolutionary and neurobiological investigations have supported the gape display as an indicator of disgust. It has been further shown that, in the absence of illness, exposure to a context previously paired with illness/toxicity elicits

anticipatory disgust and gaping in rodents. Here we consider whether social factors can also serve as cues for the display of anticipatory disgust in rats. Over 4 conditioning days (72 hours apart), 44 naïve male Long-Evans rats were intraperitoneally injected with either 128 mg/kg LiCl (0.15M) or 0.9% isotonic saline (NaCl). Each of these treatment groups was further subdivided into LiCl and NaCl-treated rats exposed to either the distinct context-only (Groups LiCl-C and NaCl-C), or exposed to the distinct context plus a specific stimulus rat (Groups LiCl+Rat and NaCl+Rat).72 hours following the last conditioning day, rats were tested over 2 drug-free test days (48 h apart). On test day 1, rats were re-exposed to the stimulus rat in a novel context for 10 minutes and active aversive behaviors were analyzed. During test day 1, a significant effect of conditioning group (social versus alone) on gaping ($p < .01$) was discovered. The mean number of gapes for the social condition, significantly differed from the mean number of gapes for the alone condition ($p = 0.013$). However, on test day 2, when the rats were placed back in the conditioning context, there were no significant differences between groups. Our results demonstrate that, in a distinct context, a rat paired with LiCl in the presence of a familiar social partner displays more gaping reactions compared to LiCl rodents paired with an unfamiliar social partner. These findings suggest that social factors can both elicit and modulate anticipatory disgust reactions.

29. **The role of corticotropin-releasing factor in mediating the effect of acute stress on effort-based decision-making.** Bryce, Courtney & Floresco, Stan. University of British Columbia. Corticotropin-releasing factor (CRF) initiates the hypothalamic-pituitary-adrenal (HPA) axis during episodes of acute stress and acts outside the hypothalamus to mediate many of the central effects of acute stress on behavior. The influence of acute stress learning and memory tasks has been well characterized and depends on a variety of factors including the context and severity of the stressor. In contrast, how acute stress influences higher level cognitive functioning, including decision-making ability, is relatively less known. Decision-making involves choosing between several alternative possibilities after evaluation of the relative costs and benefits. Increasing the amount of effort required to obtain a reward is one type of cost that can diminish the subjective value of objectively larger rewards. Repeated episodes of stress can result in depressive symptoms including anergia, which may reduce the tendency to exert effort to obtain rewards. The goal of the current study was to elucidate the underlying mechanisms of acute stress on effort-based decision-making. Using an operant chamber assay, rats were required to choose between a low effort/low reward lever (LR; 2 pellets), and a high effort/high reward lever (HR; 4 pellets), with the effort requirement increasing over trial blocks (2, 5, 10 and 20 presses). Normally rats will choose the HR lever more often when the effort cost is low, reducing their preference for this option as the amount of effort increases. Acute restraint stress, but not injection of corticosterone, caused rats to choose the HR option less compared to baseline performance. A subsequent study found that microinfusions of CRF (3 ug, ICV) decreased HR choice, mimicking the behavioral profile of restraint stress on effort-based choice behavior. This effect was not due to CRF reducing preference for the large reward because central CRF infusion no longer influenced choice when the costs of the decision were equated (1 press for 2 pellets or 4 pellets). Additionally, central infusion of the nonspecific CRF antagonist, alpha-helical CRF (30ug, ICV), prior to restraint stress, ameliorated the effect of acute stress on choice behavior. The nucleus accumbens (NAc) core plays a key role in promoting choice of high-effort/high reward options and also expresses CRF receptors. Yet, CRF micoinfusion (0.5ug) into the NAc core flattened the discounting curve, but did not recapitulate the effects of icv-CRF or restraint on decision making suggesting that this neuromodulator is acting in other brain regions (e.g. VTA) to mediate the stress-induced changes in choice behavior. Collectively these data indicate that excessive CRF release during stress may interfere with cost/benefit judgments involving effort costs. These findings may provide insight into the neurochemical mechanisms underlying anergia observed in depression.

30. **Mother rats know best: An investigation of maternal experience on cognitive and emotional resilience.** Kirk, E., Kent, M., Thompson, B., Hazelgrove, A., Bardi, M., & Lambert, K. Department of Psychology and Behavioral Neuroscience, Randolph-Macon College, Ashland VA USA. In preparation for motherhood, several neurobiological alterations that enable female mammals to meet the energy demands associated with pregnancy, parturition, and lactation have been observed. For example, maternal rats must learn how to forage more efficiently to provide nourishment for both herself and multiple offspring while avoiding predators and other threats. Accordingly, research conducted on maternal rats has indicated enhanced spatial/foraging abilities and a more resilient stress response; additionally, evidence of enhanced complexity in certain brain areas such as the hippocampus, involved in learning and memory, has been reported (Lambert & Kinsley, 2012). Given these previous findings, the current study explored problem-solving strategies and emotional resilience in maternal and virgin Long-Evans rats to provide more specific information about emotional regulation in the maternal rat. Specifically, eight post-lactational females and eight age-matched females with no reproductive experience were trained on the Dry Land Maze (DLM), a spatial learning task. Fecal samples were collected before and after training on the DLM so that corticosterone and dehydroepiandrosterone (DHEA), associated with stress and resilience, respectively, could be assessed. Following training, testing and a probe test (to assess prediction errors/cognitive uncertainty when expected reward was removed), the brains were processed for glucocorticoid and mineralocorticoid receptor-, as well as for brain-derived neurotrophic factor (BDNF)-immunoreactivity. Independent samples t-tests revealed that maternal females demonstrated more effective search strategies in the probe test (visiting more previously baited wells and exhibiting fewer escape rearing responses than their virgin counterparts); furthermore the maternal females exhibited decreased glucocorticoid receptor immunoreactive cells in the hippocampus, specifically CA1 ($p = 0.01$), a nonsignificant trend towards increased BDNF receptors in the hippocampus, specifically CA3 ($p = 0.06$), and a higher DHEA/corticosterone ratio ($p = 0.05$), all indices of effective coping and emotional regulation. In sum, rats with maternal experience exhibited cognitive persistence and emotional resilience following a challenging problem solving task. This research was supported by the Schapiro Undergraduate Research Fellowship awarded to EK.

31. **Sex Differences in Two Tests of Anxiety-Like Behavior in Rats.** Scholl, J.L., Fox, L.C., Watt, M.J., & Forster, G.L. Center for Brain and Behavior Research, Division of Basic Biomedical Sciences, University of South Dakota Sanford School of Medicine, Vermillion South Dakota. The use of animal models for behavior as well as pharmaceutical testing is employed in many different fields of research and often relies solely on male animals. Females are often overlooked in testing animal models due to concerns with how the estrous cycle will affect or complicate experiments, and the existing literature often offers inconsistent results for females regarding effects of estrous cycle. The higher prevalence of affective disorders, including anxiety and depression, in women suggests that the ability to include female animal models in studies should be an important focus. Our current study sought to confirm a baseline for behavior in two commonly employed tests of anxiety-like behavior and determine any sex differences as well as any effect of the different stages of estrous. The need to confirm findings in both social and non-social testing is important for the inclusion of females in future research. Anxiety-like behavior in male and female Sprague-Dawley rats was assessed using elevated plus maze as well as a social interaction/avoidance paradigm. Female rats were examined once daily for eight days to accurately determine their stage of estrous during the behavioral testing. Results from the elevated plus maze showed that male rats spent significantly less time on the open arms than the female rats, and when the effects of cycle were taken into account, we found that female rats in proestrous and estrous spent significantly more time on the open arms of the maze

compared to male rats. The social avoidance test revealed that female rats spent significantly less time in the interaction zone with an age- and sex-matched conspecific as compared to male rats, and this effect was not dependent on the stage of the estrous cycle. Overall, our findings confirm other results that anxiety-like behaviors differ between sexes and depend on the nature of the test used, but suggest that for these two types of tests data obtained from females could be collapsed across some of the cycle phases to facilitate the inclusion of females in behavioral experiments. Supported by NIH R01DA019921.

32. **Methylene blue enhances mitochondrial activity, functional connectivity and memory performance in rats experiencing chronic cerebral hypoperfusion.** Allison Auchter[1], F. Gonzalez-Lima[1], Marie H Monfils[1. 1]University of Texas at Austin. Chronic cerebrovascular ischemia, one of the risk factors for mild cognitive impairment (MCI) and Alzheimer's disease (AD), has been shown to diminish mitochondrial respiration and impair memory consolidation. As such, drugs that improve mitochondrial function may be appropriate treatments for cerebral hypoperfusion. Methylene blue (MB) is a historical blue dye that crosses the blood-brain barrier and serves as an electron cycler in the mitochondrial electron transport chain. Previous studies implicate MB in both memory enhancement and neuroprotection. This experiment followed a 2x2 factorial design in which rats underwent either permanent bilateral carotid occlusion (2-VO) or sham surgery (no-VO) followed by daily intraperitoneal injections of either 4 mg/kg USP MB or saline. Following recovery from surgery, subjects were trained on a visual discrimination task, whereby subjects were placed at one end of a Y-shaped water tank and allowed to swim down one of two arms to find an invisible escape platform. Distinct patterns were displayed at the end of each arm, and the location of the platform was indicated by the patterns. For 10 days, subjects were trained on three elemental pattern discriminations (A+B-, C+D-, E+F-). Though all subjects successfully learned the elemental discrimination task, 2-VO subjects treated with saline performed worse than sham subjects; 2-VO subjects treated with MB performed significantly better than saline controls. Brains were histochemically stained for cytochrome oxidase (CO) activity, an index of mitochondrial function. Whole brain quantitative CO mapping indicated widespread functional connectivity in sham subjects, particularly between hippocampus, amygdala and cortical regions. 2-VO surgery resulted in (1) decreased CO activity in hippocampus, amygdala and M2 and (2) disconnected functional activity between the amygdala and cortical regions. Treatment with MB increased CO activity in these regions as well as amygdala-cortical connectivity. Brain-behavior correlations revealed positive correlations between the similar brain regions and Y-maze performance. These results are the first to show how 2-VO affects mitochondrial functional connectivity, and how MB enhances mitochondrial activity and restores functional connectivity. Funding acknowledgement: University of Texas at Austin research grant to F. Gonzalez-Lima and NIMH (R01; R21) funds to M.H. Monfils.

33. **Motoric and Automated Home cage Assessment of a Transgenic Rat Model of Spinocerebellar Ataxia type 17 (SCA17).** Elisavet I. Kyriakou[1, 2,3], Johanneke E. van der Harst[3], Andrew J. Spink[3], Huu P. Nguyen[2], Judith R. Homberg[1. 1] Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Centre, Nijmegen, The Netherlands. [2] Institute of Medical Genetics and Applied Genomics, University of Tubingen, 72076 Tubingen, Germany. [3] Noldus Information Technology, Wageningen, The Netherlands. 'Neurodegenerative diseases' is a broad term used to describe disorders where neurons progressively die and cannot be reproduced or replaced by the body. Depending on which area of the central nervous system that is affected, different diseases develop. Although the specific symptoms vary they commonly include motoric, psychiatric and cognitive disturbances. As ageing population worldwide is increasing rapidly, and since neurodegenerative disorders are debilitating and still incurable, they constitute an important

medical and societal challenge. Spinocerebellar Ataxia type 17 (SCA17) is an autosomal dominantly inherited disease caused by a polyglutamine expansion in the TATA-box binding protein. Common symptoms include ataxia, dystonia, seizures as well as dementia and parkinsonism, in combination with psychiatric and extrapyramidal features, epilepsy and mild sensorimotor axonal neuropathy. Our aim is to characterize and validate a novel transgenic rat model of SCA17 recently established and use the valid phenotypes in preclinical treatment studies. A key aspect of the characterization work is to evaluate novel automated methods for behavioral classification and assessment of transgenic and wild type animals, as these often have a higher throughput compared to classical tests, and are thought to provide more valid behavioral readouts. This will enable the detection of early onset of specific symptoms and provide read-out parameters in pre-clinical studies. To characterize the behaviour we use a unique integrated system based on video tracking in the PhenoTyper that allows to monitor progression of symptomatology continuously. Sophisticated automated behavioral tasks will be applied to investigate in detail possible disturbances in fine motor coordination and gait (e.g using the CatWalk system), as well as the animal's locomotion pattern. CatWalk® is a useful tool for an objective and automated method to assess motor coordination and gait abnormalities providing an extensive number of gait parameters, however, it has been used so far mainly for modelling pain, sciatic nerve injury and arthritis but not so much for neurodegenerative diseases that affect locomotion, and more specifically cause ataxia. Findings from motoric and non-motor deficits of this rat model using both innovative automated tools but also standard behavioural will be presented in a descriptive manner and discussed.

34. **Consequences of two different periods of neonatal maternal separation on social behavior of adolescent male rat**. Magalhães, Ana[1,2];Nogueira, Marlene[3]; Alves, Cecilia Juliana[4,5];Mesquita, Ana[3]; Summavielle, Teresa[2,5]; de Sousa, Liliana[1. 1]ICBAS- Instituto de Ciências Biomédicas Abel Salazar, Universidade de Porto, Portugal. [2]BMC- Instituto de Biologia Molecular e Celular, Universidade do Porto, Portugal. [3]CIPsi- Center for Research in Psychology, School of Psychology, Universidade do Minho, Portugal. [4]INEB Instituto de Engenharia Biomédica, Universidade do Porto, Portugal. [5]ESTSP- Escola Superior de Tecnologia da Saúde do Porto, Instituto Politécnico do Porto, Portugal. Adverse social events early in life, including maternal separation (MS), are known to profoundly affect brain development and increase risk of attachment disorders. However, less is known about the impact of MS on adolescent social behavior. Interactions with peers become particularly important during adolescence and social peer influences are among the strongest predictors of adolescent risk-taking behaviors, such as drug use. The current study aimed to: 1) understand the impacts of short daily maternal separation, during two different periods early in life, on social behavior of adolescent Wistar rat. Since development is an ongoing process, the imprinting consequences of early adversity are highly dependent on the "time window" in which they occur. In this study we studied this issue using two different periods of maternal separation corresponding approximately in humans to period that some children initiate the nursery at age of 5 month or 3 years of age; 2) explore the ability of environmental enrichment (EE) to protect from deleterious effects of maternal separation on adolescent social behavior. The stimulation provided via EE applied early in life alters both brain and behavior and may be beneficial for the behavior development; 3) explore the expression profile of oxytocin (OT) and OT receptor, and correlate the effects of MS and EE on adolescent social behavior with the expression profile of OT and OT receptor, given its relevance for both maternal and other social behavior). In order to achieve these goals we used two periods of MS, between postnatal days PND 2 and 6 or between PND 10 and14, 2 hours daily, during which half of animals were in EE and the other half in standard environment, and the effects on male adolescent social behavior, such as social interactions with familiar and unfamiliar peer, were studied. Results showed that daily MS from PND 10 to14 did not affect social interactions with unfamiliar peer,

however affected social interactions with familiar peer by reducing the social investigation and play behavior. MS during PND 2 to 6decreased social investigation, play behavior, play solicitation and increased nonsocial activities during interaction with unfamiliar peer. Moreover, EE increase play behavior during MS from 2-6 The analyses of social interactions with familiar peer showed that MS from PND 10 to 14 reduce social investigation and play behavior, while MS during PND 2 to 6 reduce play behavior and increase nonsocial activities. Taken together, these results provide new evidence that early short periods of maternal absence is able to shape male adolescent social behaviors and highlighting that distinct social behaviors are differentially sensitive to maternal separation across ontogeny. This work was financed by FEDER funds through Programa Operacional Factores de Competitividade – COMPETE and by Portuguese funds through FCT – Fundação para a Ciência e a Tecnologia, in the framework of the project ref. PTDC/MHC-PAP/5304/2012.

35. **Individual differences in locomotor activity correlate with behavioral responses to ethanol in zebrafish: Potential roles of the dopaminergic and serotonergic neurotransmitter systems.** Steven Tran[1], Magda Nowicki[2], Arrujyan Muraleetharan[2], Diptendu Chatterjee[2], Robert Gerlai[1, 2.] [1]Department of Cell and Systems Biology, and [2]Psychology, University of Toronto. Zebrafish have been previously shown to exhibit individual differences in baseline locomotor activity (e.g. hyperactive and hypoactive phenotypes) which persists over time and across different experimental contexts. These individual differences in behavioural responses may potentially represent underlying differences in neurotransmitter systems and biochemical pathways. Furthermore, these differences may also alter how individual zebrafish respond to a drug challenge. To examine these questions we quantified baseline locomotor responses and subsequently exposed each zebrafish to either 0 or 1.0% v/v ethanol for 30 minutes. Behavioural measures including total distance traveled (cm – a measure of activity), variance of the distance to bottom (cm^2 – a measure of vertical exploration) and absolute turn angle (deg – a measure of erratic movement) were quantified and averaged over the last 10 minutes of exposure. Immediately following the acute ethanol challenge, zebrafish were euthanized and their brains dissected. The levels of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC), serotonin (5-HT), and 5-hydroxyindoleacetic acid (5-HIAA) were quantified from whole brain tissue using high precision liquid chromatography (HPLC). In addition, we calculated ratios to determine indexes of monoamine metabolism (breakdown) including dopamine turn over (DOPAC:DA) and serotonin turn over (5-HIAA:5-HT). Zebrafish that were initially classified as hyperactive exhibited a behavioural profile indicative of a less anxious phenotype and a neurochemical profile suggesting increased dopamine and serotonin metabolism. Zebrafish initially classified as hypoactive exhibited a behavioral profile indicative of a more anxious phenotype and a neurochemical profile suggesting decreased dopamine and serotonin metabolism. In response to the acute ethanol challenge, there was an overall increase in total distance traveled and a decrease in the levels of DOPAC and 5-HIAA in the brain. Behavioral and neurochemical differences between hyperactive and hypoactive zebrafish were attenuated by acute ethanol exposure. Overall, we identified significant differences in the dopaminergic and serotonergic neurotransmitter system in zebrafish which appear to correlate well with behavioral measures including locomotor activity and anxiety-like behavioral responses. Acknowledgements: Funding supported by an NSERC Discovery Grant issued to R.G. and an NSERC CGSD issued to S.T.

36. **A novel object recognition task that leads to a lasting expression of memory.** Michael J. Spinetta[1], Jessica I. Wooden[2], Mark E. Maynard[2], Charles I. O'Leary[1], J. Leigh Leasure[2,3.] [1]Department of Psychology, Seattle University, Seattle, WA 98122. [2] Department of Psychology, [3] Department of Biology & Biochemistry, University of Houston, Houston, TX 77204. Compared to other tests of memory, novel object recognition (NOR) is preferable in many cases because it does not

cause undue stress to the animal, requires no reinforcement or punishment to motivate behavior, and does not require prolonged training before it can be performed. Moreover, it capitalizes on a rodent's natural preference for novelty and an inclination to explore its environment. However, existing NOR paradigms have several shortcomings, including the potential for unintended odor cues and assessing only habituation to a novel stimulus, without robustly testing memory. The present study introduces a modified NOR task that controls for odor confounds and provides a robust test of memory. The task has three difficulty levels: Easy, Medium, and Hard. The three levels of difficulty were developed by increasing object similarity at each level, challenging rodents to distinguish accurately between objects. The intention was to assess whether lasting recognition memory would be expressed more reliably for dissimilar objects. On day 1 of the task, all rats (regardless of stimulus complexity) spent significantly more time exploring an unfamiliar wooden shape (novel object-1 (NO1)) compared to three familiar circular wooden beads previously taken from the animal's home cage. The novel wooden objects were discarded after each use, controlling for the chance that the animal's behavior was motivated by the familiarity of the object based on scent cues. Three one-minute learning trials with 1-minute inter-trial intervals (ITIs) ensured lasting memory for NO1, controlling for sensory adaptation. On day 2 of the task, rats were presented with an unfamiliar wooden object (novel object-2 (NO2), as well as NO1 and 2 familiar circular wooden beads for three one-minute trials with 1-minute ITIs. Individual differences in exploration motivation, indicated by high and low mean exploration times, was controlled for by normalizing performance to a mean percentage of exploration time. A preference for NO2 over NO1 was observed in all rats, at all three difficulties. Interestingly, while rats in the Easy paradigm habituated to baseline by the third trial with NO1 on Day 1, no similar habituation was observed in the Medium and Hard paradigms, suggesting that sustained exploration of NO1 on Day 1 had no impact on the expression of memory for NO1 the following day. This indicates that difficulty level, or the similarity in shapes, did not have an effect on overnight memory for NO1. Our results establish a simple and sensitive NOR test that eliminates odor confounds, takes less time to run than comparable tasks, and offers the flexibility of three difficulties depending on experimental needs. This work was supported by New Faculty Startup Funds for MJS from the College of Arts and Sciences, Seattle University and a Grant in Aid to JLL from the College of Liberal Arts and Social Sciences, University of Houston.

37. **Effects of aging on testosterone and androgen receptors in the male rat forebrain.** Low KL[1], Ma CQ[1], Tomm RJ[1], Tse MT[1], Grist MM[1], Floresco SB[1], Soma KK[1]. [1]Department of Psychology and the Brain Research Centre, The University of British Columbia. Although testosterone (T) has long been known for its role in sexual behaviour, recent studies show that T also plays a vital role in regulating cognition, learning, and memory. During aging there are declines in both circulating T levels and cognitive function. T might influence cognition via direct or indirect actions on the prefrontal cortex (PFC). For example, T can modulate the mesocorticolimbic dopamine system, in which dopaminergic neurons in the ventral tegmental area (VTA) project to the nucleus accumbens (NAcc) and PFC. The VTA and NAcc (and to a lesser extent, the PFC) express androgen receptors (AR). Here, in a study of young (5 months, n=12) and aged (22 months, n=12) male rats, we examined performance on working memory and decision-making tasks, T levels in serum and brain, and AR immunoreactivity in the VTA, NAcc, and PFC. Relative to young males, aged males had poorer performance on a variety of cognitive tasks mediated by the PFC and the NAcc. As expected, aged males had lower serum T levels than young males. Interestingly, in both young and aged males, T levels were higher in microdissected brain regions (VTA, NAcc, PFC) than in serum. The brain T to serum T ratio was higher in aged males than young males, suggesting compensatory upregulation of brain T synthesis in aged males. AR was detectable in VTA and NAcc, but there were no effects of age. In the mPFC, AR was not detectable using the present immunohistochemical protocol. Interestingly, young males

had more AR than aged males in the lateral orbitofrontal cortex (LOFC), a region involved in reversal learning and value-based decision-making. Altogether, these results suggest that variations in T signalling in the brain may contribute to alterations in cognitive functions that occur during aging via actions on distributed neural circuits that include the PFC, VTA, NAcc, and LOFC.

38. **Sexual interactions among rats: Who takes the initiative?** Anders Ågmo, Dag Bergheim and Xi Chu, Dept. of Psychology, University of Tromsø, Norway. For several decades it has been believed that the female controls the pace of sexual interaction. This belief partially stems from a few descriptions of rat copulatory behavior in the wild. It was mentioned that estrous females occasionally withdraw into a burrow with one or several males waiting at the entrance for the female to reemerge. However, since no actual data were reported it is impossible to determine in which proportion of sexual encounters this pattern was present. Additional support for the notion of female control comes from one study in a seminatural environment. There it was reported that about 90 % of intromissions were preceded by female paracopulatory (proceptive) behavior in the form of approach, darting and hopping. It was, therefore, concluded that female initiative is crucial for sexual interactions. This conclusion has been widely accepted. To the contrary, in the course of a series of studies in a seminatural environment we observed that male pursuit of the female often preceded sexual interactions, raising doubts about the notion of female control. Therefore, we decided to make an extensive analysis of the male and female behavior patterns preceding sexual interaction in a seminatural environment. We used data from 5 groups, each consisting of 4 intact, cycling females and 3 intact males. All sociosexual interactions during the females' period of behavioral estrus were recorded. We then identified a total of 5370 episodes of paracopulatory behavior and determined the male behavior pattern displayed during a period extending from 10 s before to 10 s after the episode. It was found that43 % of paracopulatory behaviors were preceded by male pursuit, and 34 % followed by a copulatory act. Of all episodes of male pursuit, 38 % were preceded by paracopulatory behavior and 25 % followed by a copulatory act. If, instead, we analyze the behavior preceding a copulatory act it turns out that 97 % of all copulatory acts followed paracopulatory behavior and 85 % followed male pursuit. This is possible because pursuit and paracopulatory behavior usually overlap, although one of them is initiated shortly before the other. These data show that the male and the female are equally important for initiating sexual interactions. This fact has considerable importance for the interpretation of data from studies of the neuroendocrine control of male and female sexual behavior.

39. **Acetylcholine signaling at muscarinic receptors is necessary for social learning in female mice.** Kelsy Ervin, Melanie Sawula, Pietro Paletta, and Elena Choleris. Dept. of Psychology and Neuroscience Program, University of Guelph, Guelph, ON N1G 2W1 Canada. Animals living in social groups, including humans, have the advantage of learning from conspecifics, rather than through costly and potentially risky trial-and-error learning. This phenomenon of social learning can be studied in rodents using the social transmission of food preferences (STFP). In this task, an "observer" animal interacts with a "demonstrator" that has recently consumed a novel-flavoured food. When later given a choice of two or more novel foods, the observer tends to prefer the novel food it smelled on the demonstrator's breath. In male rats, the STFP has been shown to depend upon acetylcholine signaling (Boix-Trelis et al, 2006, Learn Mem 13:783; Berger-Sweeney et al, 2000, Hippocampus 10:729; Ross et al, 2005, Learn Mem 12:302), specifically through muscarinic receptors (mAChRs) (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). However, the involvement of acetylcholine in the STFP in female animals and in mice has not yet been investigated. We therefore treated female, ovariectomized CD1 mice with 1, 2, or 3mg/kg of the mAChR antagonist scopolamine or saline vehicle intraperitoneally 30min prior to a 10min videotaped interaction with a same-sex

ovariectomized demonstrator. Observers were tested for food preference immediately after the interaction, with food intake measured at the 30min and 2, 4, 6, and 8h intervals of the choice test. The highest dose of scopolamine, 3mg/kg, blocked expression of a socially acquired food preference, indicating that mAChRs are necessary for social learning in female mice. These results add to the current literature and provide further avenues for research on the mechanisms and brain regions involved in social learning in male and female animals. Funded by a grant from the Natural Sciences and Engineering Research Council of Canada (NSERC).

40. **A change of heart: Mapping coping style phenotypes to cardiovascular and neurobiological responses associated with emotional regulation in male and female rats *(Rattus norvegicus)*.** Thompson, B., Kent, M., Kirk, E., Bardi, M., & Lambert, K. Department of Psychology and Behavioral Neuroscience, Randolph-Macon College, Ashland VA USA. Although rodent models of stress have revealed valuable information about the etiology of psychiatric disorders and other health threats, most of this research has been conducted on males, limiting informed generalization to females. Accordingly, in the current study, neurobiological and cardiovascular stress responses and resilience measures were evaluated in young Long Evans male and female rats profiled as passive, active, or flexible copers. All animals were exposed to three consecutive days of a three minute swim stress test and, the following week, 15 minute restraint stress sessions during which cardiovascular measures were assessed. Additionally, fecal samples were collected to assess Corticostereone (CORT) and Dehydroepiandrosterone (DHEA), as well as the DHEA/CORT ratio at various time points. Subsequently, brains were processed for Neuropeptide Y (NPY)-immunoreactivity in the amygdala and glucocorticoid receptors (GR)-immunoreactivity in the hippocampus. Analyses revealed that males were more active in the swim test (i.e., increased head shakes and diving responses). Additionally, regardless of sex, active coping rats had a higher Index of Cardiovascular Activity (ICA; including blood pressure, heart rate, blood flow, and blood volume measures) during restraint stress. Focusing on hormones, the active rats had higher CORT levels than the passive and flexible coping rats on day three of the swim test; additionally they had the highest CORT levels across all days of swimming assessment. Further, collapsing across coping profile, females exhibited higher CORT levels than males. Flexible copers had the highest DHEA/CORT ratio, previously associated with adaptive responding. For the brain measures, no statistically significant effects of sex or coping strategy for either NPY- or GR-immunoreactive cells were observed. In sum, the heightened cardiovascular activity and increased CORT levels observed in the active coping rats and higher DHEA/CORT ratios in the flexible copers provide additional evidence that predisposed coping strategies influence subsequent stress and resilience responses. Overall, both sex and coping phenotypes influenced behavioral, cardiovascular and endocrine responses to acute stressors in the current study; however, the coping phenotype appeared to have a more powerful impact on emotional responsiveness. Additional research is necessary to further explore the impact of these variables on the emergence of health threats such as depression symptoms and cardiovascular disease. This research was supported by the Schapiro Undergraduate Research Fellowship awarded to BT.

41. **Subtypes of prefrontal cortical NDMA receptors in working memory and normal aging.** McQuail, JA[1]; Beas, BS[1]; Simpson, K[1]; Setlow B[2]; Bizon, JL[1]. [1]Dept of Neuroscience, [2]Dept of Psychiatry, University of Florida, Gainesville FL. NMDA receptor (NMDAR)-dependent persistent firing of pyramidal neurons in the prefrontal cortex (PFC) is a likely neurophysiological correlate of working memory. NMDARs are tetramers comprised of an obligate NR1 subunit that variously associates with NR2A or NR2B subunits. These subunits confer unique channel properties as well as differ in relative abundance between PFC pyramidal neurons and interneurons. However, the contribution of specific NMDAR subtypes to working memory and their changes with age are not well

understood. To address these questions, the present study combined behavioral analysis of a delayed response (DR) task that is PFC-dependent and sensitive to aging with pharmacological and molecular approaches in young adult (6 months) and aged (22-24 months) F344 rats. Experiment 1 evaluated behavioral consequences of intra-PFC administration of NMDAR antagonists to young adult rats during DR task performance. The NR2B-preferring antagonist Ro-25 6981 produced a significant delay-dependent interaction, impairing accuracy at long delays (>18 s) relative to vehicle. The NR2A-preferring antagonist NVP-AAM077 also significantly impaired accuracy relative to vehicle but there was no interaction with delay. Experiment 2 used Western blotting methods to measure NMDAR subunit levels in PFC homogenates prepared from young adult and aged rats previously tested on the DR task. NR1, NR2A and NR2B subunit expression was lower in aged compared to young and NR2A protein positively correlated with DR accuracy. Apart from marginal reductions in AMPA receptor subunit levels, there were no other age-related changes in synaptic, spinous or dendritic proteins. The present experiments demonstrate that blockade of specific subclasses of NMDAR within the PFC produces significant, but distinct, impairments in performance on a rodent working memory task. Moreover, attenuated expression of PFC NMDARs coincides with onset of age-related working memory deficits and loss of NR2A subunit predicts severity of working memory impairment. Jointly, these studies support a vital role for PFC NMDARs in executive function and further suggest that NMDAR dysfunction may be a causal factor for working memory impairments that are prevalent among older individuals. Ongoing work will determine if positive modulation of NMDARs restores working memory in aged rats and evaluate age-related changes to NMDAR subunit:protein interactions. Supported by AG029421 and McKnight Brain Research Foundation (JLB) and McKnight Brain Institute (JAM).

42. **Exploration of the role of GTF2i in the social phenotypes of Williams Beuren Syndrome and Autism Spectrum Disorder.** Loren A. Martin[1], Erica Iceberg[1], Megan Rahman[1], Breanna Lum[1], Amy Patterson[1]. Azusa Pacific University. Williams Beuren Syndrome (WBS) is a developmental disorder caused by a deletion of human chromosome 7q11.23 that contains 26 genes. Symptoms of WBS include mild to moderate intellectual disability and hypersocial behavior. Autism Spectrum Disorder (ASD) is a behaviorally-defined collection of syndromes of known and unknown etiology that share a common phenotype including impairments in social motivation. The hypersocial behavior associated with WBS appears opposite to the hyposociality observed in ASD, and interestingly, duplications of 7q11.23 have been associated with ASD. The social phenotype of WBS has recently been linked to the deletion of a single gene: *GTF2i,* or general transcription factor IIi (TFII-I). Duplication of *GTF2i* has also recently been associated with ASD, suggesting that it works in a dosage-type response in its effects on social behavior. In this study, we characterized the specific aspects of social behavior that are modulated by GTF2i. Specifically, we compared mice having either a deletion (*Gtf2i*$^{+/-}$) or duplication (*Gtf2i*$^{+/Dup}$) of *Gtf2i* to wildtype (WT) littermate controls on a series of social behavior tasks. In the social choice task, *Gtf2i*$^{+/-}$ mice showed a significant preference for a stimulus mouse that was not observed in WT siblings. During a social encounter, *Gtf2i*$^{+/-}$ mice spent significantly more time in nose-to-nose contact compared to WT siblings. To assess social motivation, test mice were trained to press a lever for a social reward in the form of 15s access to an unfamiliar stimulus mouse. The number of lever presses achieved in the final trial of a testing session was used as an index of social motivation. *Gtf2i*$^{+/-}$ mice demonstrated significantly higher numbers of lever presses than WT mice. Results from tests comparing *Gtf2i*$^{+/Dup}$ mice to WT sibling controls are currently underway and will be presented as well. Overall, results from the tests on the *Gtf2i* deletion mice support a role for this gene in the hypersocial phenotype of WBS. Opposite results from *Gtf2i* duplication mice will support a role for this gene in the hyposocial phenotype of ASD and help establish GTF2i as a modulator of social behavior.

43. **Cognitive impairments in a mouse model of 16p11.2 deletion syndrome.** Mu Yang, Freeman Lewis, Gillian Foley, Jacqueline N. Crawley. Department of Psychiatry and Behavioral Sciences, University of California Davis School of Medicine, Sacramento, CA. Up to 1% of patients with a ~600kb deletion in the human chromosomal region 16p11.2 have autism. 16p11.2 deletion is also associated with speech delay, intellectual impairment, and developmental delays. Two mouse models of 16p11.2 deletion syndrome were independently generated. Both models exhibited low body weight, perinatal mortality, and sporadic motor stereotypies. We previously reported that juvenile and adult 16p11.2 +/- mice exhibited normal general health, neurological reflexes, responses to social and non-social odors, motor learning, normal social approach, normal juvenile reciprocal social interaction, impaired social vocalization during male-female interaction, and a novel object recognition deficit. The present study was designed to replicate the initial finding of novel object recognition deficits, and evaluate the generalization of cognitive deficits in 16p11.2 mice as compared to wildtype littermates across a range of assays: a) preference for social novelty and object location memory as corroborative measures of novelty recognition, b) acquisition and reversal learning of a pairwise visual discrimination task using the Bussey–Saksida operant touchscreen equipment as a measure of cortical dependent recognition learning and memory, and c) contextual and cued fear conditioning as a measure of emotional learning and memory. Robust novel object recognition deficits were replicated in the current cohort of 16p11.2 +/- mice. Similar deficits were found in object location memory test. 16p11.2 +/- mice did not exhibit preference for social novelty when presented with a familiar versus an unfamiliar 129Sv/ImJ mouse, indicating deficits in social recognition. Fear conditioning was normal in three cohorts of +/- mice. In the touchscreen test, 16p11.2 +/- required significantly more training days than +/+ to reach the criterion during the acquisition phase, and half of the +/- failed to reach the criterion at the 30-day cut-off of the reversal phase, indicating learning deficits and cognitive inflexibility. These phenotypes support the use of 16p11.2 deletion mice as a model for aspects of intellectual disabilities in 16p11.2 deletion patients with autism.

44. **Investigation of dual orexin receptor antagonism on cocaine reward and initial positive affective reactivity to cocaine in rats.** Steven J. Simmons[1]; Taylor A. Gentile[1]; David J. Barker, Ph.D.[2]; John W. Muschamp, Ph.D.[1, 1] Center for Substance Abuse Research (CSAR); Temple University School of Medicine; Philadelphia, PA, 19140. [2] National Institute on Drug Abuse (NIDA); Integrative Neuroscience Branch, Neural Networks Division; Baltimore, MD, 21224. Substance abuse remains a major health and economic problem, leading to premature death and costing $181 billion annually in health care, crime, and lost productivity costs. Strikingly, no pharmacotherapies are currently available to effectively treat psychostimulant dependence. Psychostimulants cause changes in neural circuits involved in reward and affect, but addiction neurocircuitry is incompletely understood and new targets for therapeutic intervention are needed. Recently, rodent studies have demonstrated a role of lateral hypothalamic orexins (‘hypocretins’) in motivated behavior and reward processing. Further, orexin G-protein coupled receptors 1 and 2 (Ox1R and Ox2R, respectively) are densely expressed in mesolimbic substrates, including ventral tegmental area (VTA) and amygdala, and orexins have been shown to modulate accumbal dopamine release. These lines of evidence and others suggest that OxR antagonism may be therapeutic for psychostimulant dependence. The present study was conducted to examine effects of suvorexant, a recently FDA-approved dual orexin receptor antagonist (DORA) on conditioned reward using a biased, forced-choice cocaine conditioned place preference (CPP) procedure. Animals were initially placed in a two-compartment shuttle box to establish natural preference. Eight daily, 30-minute conditioning trials proceeded. Animals were pre-treated with either suvorexant (30 mg/kg, i.p.) or vehicle, followed by either cocaine (10 mg/kg, i.p.) or vehicle and placed in Context A (preferred; 4 trials) or Context B (non-preferred; 4 trials), respectively.

Animals were subsequently tested for 30 minutes. Further, ultrasonic vocalizations (USVs), previously used in preclinical studies of substance abuse for their utility in reflecting opposing affective states, were recorded. CPP scores revealed that cocaine induced CPP compared to controls, but that suvorexant pretreatment prevented significant cocaine CPP. USVs revealed that suvorexant pretreatment significantly reduced initial positive affective reactivity to cocaine. Moreover, a within-groups analysis suggested that suvorexant may delay the onset of and peak affective reactivity from initial cocaine administration. This study is the first to our knowledge to examine effects of suvorexant in a preclinical model of substance abuse. Our findings suggest that DORAs may delay and attenuate cocaine-induced euphorogenesis. As motivated behavior is mediated in part by both OxR subtypes, future studies should: (i) examine effects of suvorexant on cocaine self-administration behaviors, such as progressive-ratio break points, (ii) determine relationships between USVs and serum levels of cocaine and/or examine effects of suvorexant on cocaine metabolism, and (iii) elucidate and phenotype orexinergic circuits mediating motivated behavior for and affective processing of drug rewards.

45. **Dopamine agonist ropinirole medication increases gambling behaviours in a 6-OHDA rat model of Parkinson's disease.** Tremblay, Melanie[1]; Silveira, Mason[1]; Adams, Wendy[1]; Winstanley, Catharine[1]. [1]University of British Columbia. Parkinson's Disease (PD) is a debilitating neurological disorder affecting about 1% of the aging demography and is the second most common disorder after Alzheimer's disease in this population. In humans, PD is characterized by motor impairments and cognitive deficits may also appear as the disease advances. The disease is associated with the progressive loss of dopamine neurons in the basal ganglia. Animal models using toxins that target dopamine neurons, such as the dorsolateral striatal 6-hydroxydopamine (6-OHDA) lesion model, may parallel some of the neurological damage observed in the disease and allow for behavioural testing. Selective dopamine agonist drugs that act on the $D_{2/3}$ receptor family, such as ropinirole, can successfully treat the motor symptoms of PD. However, treatment with these drugs can also lead to a variety of serious impulse control disorders (ICD), including pathological gambling, in about 16% of patients, and this may be an underestimation. In a previous experiment, we have shown that chronic ropinirole administered to normal rats increased choices of the uncertain lever in a Betting task. The Betting task measures decision-making involving uncertainty in which rats choose between a guaranteed reward versus a 50:50 chance of double that reward or nothing by pressing a lever. This time, we repeated chronic ropinirole administration on a 6-OHDA model of PD in older rats performing the Betting task. Although there was no effect of the lesions themselves of gambling behaviour, we still observed an increase in choice of the uncertain option on the task in rats receiving chronic ropinirole. These results, in conjunction with our previous observations, suggest that the neurological loss in PD patients does not play a role in the bias towards uncertainty and development of gambling and other risk-taking behaviours observed in some patients on dopamine agonist therapy. This research may help further our understanding of the maladaptive gambling behaviour experienced by PD patients treated with dopamine agonist therapy.

46. **Involvement of PI3K/Akt signaling pathway and its downstream intracellular targets in the antidepressant-like effect of creatine.** M.P. Cunha[1], J. Budni[2], F.Ludka[3], F. L. Pazini[1], J.M. Rosa[1], A. Oliveira[1], C.I. Tasca[1], A.L.S. Rodrigues. [1]Department of Biochemistry, Center of Biological Sciences, Universidade Federal de Santa Catarina, Florianópolis, Brazil. [2]Programa de Pós-Graduação em Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil. [3]Department of Pharmacy, Universidade do Contestado, Canoinhas,SC, Brazil. Creatine has been proposed to exert beneficial effects in the management of depression, but the cell signaling pathways implicated in its antidepressant effects are not well established. Taking into account the significant

role of Akt modulation in the mechanisms underlying antidepressant responses and in an attempt to advance our understanding about the mechanisms implicated in the antidepressant-like effect of creatine, the present work investigated the involvement of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway and its downstream intracellular targets: glycogen synthase kinase 3 β (GSK3β), heme oxygenase-1 (HO-1), and mammalian target of rapamycin (mTOR) in the antidepressant-like effect of creatine in the tail suspension test (TST). The acute treatment of mice with creatine (1 mg/kg, po) increased the Akt and P70S6K phosphorylation, as well as HO-1, glutathione peroxidase (GPx) and postsynaptic density protein 95 (PSD95) immunocontents in the hippocampus. The pretreatment of mice with LY294002 (10 nmol/mouse, icv, PI3K inhibitor), wortmannin (0.1 μg/mouse, icv, PI3K inhibitor), zinc protoporphyrin (10 μg/mouse, icv, HO-1 inhibitor), or rapamycin (0.2 nmol/mouse, icv, mTOR inhibitor) prevented the antidepressant-like effect of creatine (1 mg/kg, po) in the TST. In addition, the administration of subeffective dose of either the selective GSK3β inhibitor AR-A014418 (0.01 μg/mouse, icv), the non-selective GSK3β inhibitor lithium chloride (10 mg/kg, po) or the HO-1 inductor cobalt protoporphyrin (0.01 μg/mouse, icv), in combination with a subeffective dose of creatine (0.01 mg/kg, po) reduced the immobility time in the TST as compared with either drug alone. No treatment caused significant changes in the locomotor activity of mice, indicating that the behavioral responses in the TST were independent of locomotor effects. These results indicate that the antidepressant-like effect of creatine in the TST depends on the activation of Akt, Nrf2/HO-1, GPx, mTOR, and P70S6K as well as GSK3β inhibition. These data reinforce the notion that phosphorylation of Akt with the consequent modulation of its downstream proteins could be of relevance as therapeutic targets for the treatment of depression. Financial support: CNPq, CAPES (Brazil)

47. **Decreased anxiety and enhanced fronto-hippocampal connectivity in the Prrxl1 knockout mouse model of congenital hypoalgesia.** Clara Monteiro[1,2], Helder Cardoso-Cruz[1,2], Margarida Dourado[1,2], Deolinda Lima[1,2], Vasco Galhardo[1,2.] 1. Departamento de Biologia Experimental, Faculdade de Medicina, Universidade do Porto, 4200-319 Porto, Portugal. 2. Instituto de Biologia Molecular e Celular - IBMC, Universidade do Porto, 4150-180 Porto, Portugal. The comorbidity of psychiatric disorders in chronic pain patients is particularly frequent, and the reasons for this effect are still far from understood. The large prevalence of anxiety related disorders (such as insomnia, depression, post-traumatic stress disorder - PTSD, and other mood alterations) alongside pain highlight the broad disruption of emotional balance that is characteristic of painful syndromes. Although the comorbidity of psychiatric disorders in chronic pain is commonly attributed to stress-related disruption of emotional balance, the interplay between pain and stress has never been studied in a case of decreased pain perception. To address if a stress-related benefit would come from reduced pain experience, we tested the performance of Prrxl1-/- mice - a knockout model of congenital mild hypoalgesia - in behavioral tasks of attention, memory, anxiety, and fear, while recording the neurophysiological functional connectivity between prefrontal cortex and dorsal hippocampus. Prrxl1 (paired-related homeobox protein-like 1) is a transcription factor of the homeodomain family that is mainly expressed during the embrionary development of primary somatosensory neurons and their target neurons. Prrxl1-/- mice present a decreased number of small DRG neurons and alterations in the adult morphology of the superficial layers of the spinal cord, which causes a diminished sensibility in the responses to nociceptive stimuli. In this study, we quantified the forebrain expression of stress-related genes in the knockout animals. The behavioral testing of Prrxl1-/- mice revealed that these animals have enhanced attentional and working memory performance, resistance to PTSD, reduced anxiety levels and low levels of circulating corticosterone. Neurophysiological recordings showed altered theta- and gamma-band alterations in the fronto-hippocampal connectivity. The profile of forebrain gene expression show changes in the mRNA levels

of stress-related genes - namely those belonging in the corticotropin-releasing factor family. Finally, modulation of the circulating levels of corticosterone partially reversed the behavior and neural activity of Prrxl1-/- mice. Our results show that the congenital reduction of peripheral nociceptive afferents has a beneficial effect in the stress response system, highlighting the dynamic relationship between stress and pain. Supported by FCT Grants SFRH/BD/70522/2010, SFRH/BPD/92203/2013 and PTDC/NEU-SCC/1516/2012.

48. **Impact of adolescent ethanol exposure and adult amphetamine self-administration on evoked striatal dopamine release in rats.** L. Granholm, S. Rowley, M. Ellgren, L. Segerström, I. Nylander. Neuropharmacology, Addiction and Behaviour, Dept. Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. Adolescents commonly consume alcohol in a binge-like pattern and excessive use at an early age is associated with risk for substance use disorders. The dorsal striatum is involved in transition from recreational to habitual alcohol consumption but the long-term impact of adolescent alcohol exposure upon this region remains unclear. The aim in this study was to characterise and describe relationships between adolescent ethanol exposure, dopamine dynamics in dorsal striatum and adult voluntary drug intake in Wistar rats. Ethanol (2 g/kg) or water was administered intragastrically in a binge-like regimen (three continuous days/week) between four and nine weeks of age. In adulthood, animals were divided into two groups. In the first, dorsal striatal potassium-evoked dopamine release was examined via chronoamperometry, in the basal state and after a single amphetamine challenge (2 mg/kg, i.v.). In the second, amphetamine self-administration behaviour was studied (i.e. fixed and progressive ratio) before chronoamperometric analysis was conducted as described above. Adolescent ethanol exposure suppressed locally evoked dopamine response after an amphetamine challenge in adulthood whereas in the basal state, no differences in dopamine dynamics were detected. Ethanol-exposed animals showed no differences in adult amphetamine self-administration behaviour but had a more efficient removal of released dopamine after the self-administration period. The results show that adolescent binge-like alcohol exposure induces long-lasting alterations in adult dorsal striatal dopamine dynamics that are revealed after amphetamine challenges. The altered drug response relates to reduced availability of synaptic dopamine in alcohol-exposed animals that, in turn, may affect habit formation and contribute to increased risk for substance use disorders as a consequence of adolescent alcohol.

49. **Effects of early-life adversity and prenatal alcohol exposure on object recognition memory in male and female adolescent rats**. Holman, Parker J.; Haghighat, Sepehr; Raineki, Charlis; Weinberg, Joanne. Department of Cellular & Physiological Sciences, University of British Columbia, Vancouver, BC Canada V6T 1Z3. Environmental factors early in life can dramatically impact the development of learning and memory. Prenatal exposure to alcohol, for example, has been shown to impair learning and memory; moreover, early-life adversity also promotes long-term deficits in learning and memory. This has particular relevance for individuals with prenatal alcohol exposure (PAE), as they are disproportionately vulnerable to experiencing early-life adversity; accordingly, it may be difficult to separate effects of PAE from those of early-life adversity. In the present study, we assessed learning and memory using a novel object recognition task in a well-established rat model of PAE in conjunction with a model of early-life adversity to begin to dissect the unique and/or synergistic contributions of each insult. Previous studies suggest object recognition abilities in adulthood do not differ between control and PAE animals. Here, we take a developmental approach to assess object recognition earlier in development, assessing male and female rats during early (postnatal day 30) and late (P45) adolescent development.Pregnant rat dams were assigned to: 1) PAE: access to liquid ethanol diet *ad libitum*; 2) Pair-Fed: access to liquid control diet yoked to consumption of a PAE partner; or 3) Control: access to control diet *ad libitum*. From P8-12, half the

dams were provided with insufficient nest bedding, which increased abusive-like maternal behaviors such as rough handling of and stepping on pups and reduced arch-backed nursing. Offspring were evaluated using a simple object recognition test at P30 or P45. Testing occurred on two consecutive days and consisted of a familiarization phase (5-min) and a discrimination phase (5-min; novel vs. familiar object) separated by a 15-min retention period, with investigation of each object recorded. Preliminary data indicate sexually dimorphic effects of PAE and early-life adversity on object recognition tested at P30. While females exhibited robust recognition abilities regardless of prenatal treatment or early-life adversity status, early-life adversity prevented object recognition abilities in PAE males at P30, but not at P45. Taken together, these data indicate males and females are differentially sensitive to PAE and early-life adversity, with males showing enhanced vulnerability to early-life perturbations. Supported by NIH/NIAAA R37 AA007789 and R01 AA022460, NeuroDevNet (Canadian NCE) to JW, and Canadian Foundation on Fetal Alcohol Research to JW and CR; NIH/NIAAA F31 AA023151 to PJH; PJH is a NeuroDevNet Trainee.

50. **Early appearance of cognitive impairment in a mouse model of depression is associated with altered synaptic plasticity and enhanced hippocampal GluA1 expression.** Izhak Michaelevski[1,2], Moshe Gross[1,3], Anton Shenina[1,2], Elimelech Nesher[3], Tatiana Tikhonov[3], Danny Baranes[3] and Albert Pinhasov[3]. [1]Department of Biochemistry and Molecular Biology, Tel-Aviv University, Tel-Aviv, Israel; [2]Sagol School of Neuroscience, Tel-Aviv University, Tel-Aviv, Israel, [3]Department of Molecular Biology, Ariel University, Ariel, Israel. Memory deficit is a common manifestation of age-related cognitive impairment, of which depression is a frequently occurring comorbidity. In turn, depression has been identified as a risk factor for cognitive impairment and the development of dementia with age. The present study made use of the previously validated Submissive (Sub) mouse model of depressive-like behavior to identify functional correlates of aging-related cognitive impairment. Using learning paradigms testing hippocampus-dependent spatial and non-spatial memory, we demonstrate here that Sub mice developed cognitive impairments at earlier age (3 months), compared to wild type (wt). Furthermore, acute hippocampal slices from Sub animals failed to display paired-pulse facilitation, while primed burst stimulation-induced long-term potentiation (LTP) in the hippocampus was enhanced significantly relative to control. Changes in synaptic plasticity were accompanied by markedly reduced hippocampal mRNA expression of Insulin-like Growth Factor (IGF-1) and Brain-Derived Neurotrophic Factor (BDNF). Finally, the protein level of the AMPA receptor subunit GluA1 was markedly elevated in the hippocampi of Sub mice, which was exacerbated with age. In summary, our study clearly demonstrated linkage between depressive-like behavior and propensity to develop age-related cognitive impairment. Furthermore, insufficient expression of essential factors regulating synaptic plasticity linked to a depressive-like phenotype may affect AMPAR-based glutamate neurotransmission, leading to the development of cognitive impairment with age.

51. **Cystatin F gene ablation exacerbates the status of demyelination in cuprizone model mice.** Junjie Liang1, Ning Li1, Kai Fan1, Yanli Zhang1, Ikenaka Kazuhiro2, Jianmei Ma1. Department of Anatomy, Dalian medical university, Dalian, Liaoning, China 116044. Division of Neurobiology and Bioinformatics, National Institute for Physiological Sciences, Okazaki Aichi 444-8787, Japan. Demyelinating process is usually accompanied by changes of various gene expression in demyelinating diseases such as multiple sclerosis (MS), and these genes may be involved in the pathogenesis or progression of the diseases. In our previous studies, we scanned differential expression genes by using cDNA microarray in demyelinating animal model. Among numerous differential expression genes, cystatin F gene was selected for further study because of its special expression manner. Cystatin F belongs to the cystatin superfamily of papain-like lysosomal cysteine proteinase inhibitors. We found the cystatin F expression in microglia/macrophages during the stages

of ongoing demyelination/remyelination in both MS animal model and MS patients. However, so far the functional role of cystatin F in demyelinating process has not been made clear. In this study, we used cystatin F knock out (KO) mice to create the cuprizone-induced demyelination animal model to clarify its functional role and the molecular mechanism involved in demyelinating process. We found that the status of demyelination in cystatin F KO mice was significantly more severe than that in wild type mice, and more robust micrglia/macrophages and leukocytes were found accumulated in demyelinating areas. Simultaneously, the expression of cathepsin C which is the main inhibiting substrate of cystatin F was significantly higher. Because it has been found that cathepsin C affected the expression level of $CXCL_2$ in inflammatory diseases of peripheral system and $CXCL_2$ can be induced by glial cells in the CNS, we studied the expression levels of $CXCL_2$ mRNA and protein in both cuprizone-treated wild and cystatin F KO mice by real-time quantitative PCR and ELISA. We found significantly higher $CXCL_2$ level in cuprizone-treated cystatin F KO mice. Furthermore, in*in vitro* experiments we found exogenous cathepsin C can stimulate the glial cells to product more $CXCL_2$. Therefore, we supposed that ablation of cystatin F gene resulted in loss of its inhibition of cathepsin C activity, which could up-regulate the expression of $CXCL_2$ leading to more inflammatory cells infiltration. In order to testify our hypothesis, we used conditional cathepsin C overexpression (OE) mice to create the cuprizone model again. As expected, more infiltrating leukocytes were detected in cathepsin C OE mice and demyelinating status was significantly more severe than that in wild type mice. In summary, ablation of cystatin F resulted in loss of its inhibition of cathepsin C activity, which could up-regulate the expression of $CXCL_2$ leading to more inflammatory cells infiltration, finally aggravate the status of demyelination. Thus, inhibiting the activity of cathepsin C may be one of the hopeful strategies for neuroinflammatory diseases. (This work is supported by NSFC grant NO. 81271322)

52. Involvement of opioid signaling in food preference and effort-related decision making in rats I. Morales[1], E. Brockway[1], J. Selva[1], H. Baumgartner[1], L. Zallar[1], P. Currie[1], T. Hackenberg[1], R. Pastor[1,2]. Department of Psychology, Reed College, Portland, OR. Area de Psicobilogía, Universitat Jaume I, Castellón, Spain. Motivation is a complex process that involves appetitive and consummatory phases. Opioid receptor antagonists decrease operant responding for food on progressive (PR) ratio schedules, indicating that this system is involved in appetitive, instrumental behavior. Opioid signaling has also been suggested to mediate consummatory behavior by altering palatability and hedonic responses. The present study examined the role of opioid receptors in food reinforcement using an effort-related decision-making task, (i.e., a progressive ratio/chow feeding choice task). With this task, rats can choose between working for a preferred food (high-carbohydrate banana-flavored pellets) by lever pressing on a PR schedule vs. obtaining a less preferred laboratory chow that is freely available concurrently in the chamber. Naloxone (0, 1.5, 3.0 mg/kg; i.p.) decreased the highest ratio achieved and number of reinforcers earned, but had no effect on the amount of chow consumed. A similar task (fixed ratio 5; FR5/Chow) was used to study the generalizability of naloxone's effects under a less effort-demanding schedule; naloxone (3.0 mg/kg) decreased responding and the number of reinforcers earned, but no reduction in chow intake was found. Finally, a preference test measured the relative intake of both foods (banana pellets vs. chow) under effort-free conditions. Opioid receptor blockade (naloxone, 3.0 mg/kg) selectively reduced banana pellet intake but had no effect on chow. The present findings support evidence suggesting that opioids selectively affect intake of relatively preferred foods. For preferred foods, both appetitive and consummatory aspects of motivation seem to be mediated by opioid receptors. Our results argue against a general suppression of appetite by naloxone as appetite manipulations have been shown to alter intake of both types of foods. Naloxone's effects on the present tasks can be contrasted with

those of dopaminergic manipulations, which reduce operant responding but cause compensatory increases in chow, and do not affect food preference when tested in effort-free conditions.

53. **An animal model of recurrent depression: investigating potential mechanisms of depressive episode recurrence.** Katherina Lebedeva[1], Erin Fenton[1], Rudy Bowen[1], Hector Caruncho[1], Lisa Kalynchuk[1]. [1]University of Saskatchewan, Saskatoon, Canada. Major depression is a chronic and recurrent condition. Depressive episodes become easily triggered over time, and each episode increases the probability of the subsequent onset. However, the existing preclinical models of depression do not address the sensitization developing over the course of multiple episodes. We have proposed a new animal model of recurrent depression and investigated the potential mechanisms underlying the cyclical nature of depression. Methods: We assessed depression-like behavior in rats through 3 cycles of treatment with the stress hormone corticosterone (CORT). Each cycle of treatment comprised 21 days of CORT injections (20 mg/kg) followed by 21 days of recovery. The behavior was recorded in the middle and end of each CORT treatment and at the end of each recovery period via the forced swim test (FST) and the sucrose preference test (SPT). Open field test was conducted to assess the general locomotor activity. Brain tissue was analyzed for changes in Doublecortin (DCX) and RE1-silencing transcription factor (REST) expression in the hippocampus. Results: CORT administration produced increasingly greater effects on depression-like behavior in rats. In the 1st cycle, CORT increased immobility behavior after 21 days of treatment, which then normalized after the recovery period. In the 2nd and 3rd cycles however, CORT induced an early manifestation of depression-like behavior after only 10 days of treatment. Furthermore, CORT-treated rats showed increasingly greater anhedonia-like behavior with each cycle. No differences were found in general locomotor activity between treatment groups. In addition, CORT produced physiological alterations indicative of depression: decreased body weight gain (1st cycle) and body weight loss (2nd and 3rd cycles). We found a transient increase in the number of REST+ cells in several hippocampal areas in CORT rats after the 1st cycle of treatment, however, after 3 cycles, REST levels were decreased compared to control rats. Finally, we observed accumulative decreases in the number and dendritic complexity of immature DCX+ neurons in the dentate gyrus of CORT rats. These results may suggest accelerated brain ageing and compromised brain's stress response system as potential neurobiological mechanisms of recurrent depression.

54. **Obesity and binge eating are associated with heightened negative affect and desire to eat, but not hunger, following mental stress: preliminary evidence.** Rebecca Klatzkin, Sierra Gaffney, LauraLee Madigan, Caroline Sumner, Allie Baldassaro, Saniya Rashid. Rhodes College. Over one-third of adults in the United States are obese, indicating the need for a greater understanding of the physiological and psychological underpinnings of obesity. Stress has been implicated in the etiology of both obesity and Binge Eating Disorder (BED). The release of glucocorticoids following stress increases appetite as well as the preference for comfort foods, a combination of factors that nurture the development of binge eating and obesity. Negative affect has been proposed as a mechanism underlying stress-induced eating. While both negative affect and hunger increase the rewarding properties of food, stress-induced intake of palatable food has been shown to occur in the absence of hunger, particularly in individuals with high disinhibition of dietary restraint. The present study attempted to build on these findings by investigating whether binge eating psychopathology and body mass index (BMI) were more strongly associated with psychological measures of negative affect and desire to eat, as opposed to homeostatic hunger, following mental stress. Thirty-two female undergraduate students (BMI = 24.3 ± 4.1) underwent the Trier Social Stress Task (TSST), consisting of a speech and math stressor. Oral contraceptive use served as a covariate in all analyses. Both the speech and math portions of the TSST induced significant increases in SBP, DBP, and HR from

baseline, ps < .001. Higher scores on the Binge Eating Scale (BES) were associated with increases in negative affect from baseline to mental stress, r = .36, p<.05. Stress-induced increases in desire to eat, but not hunger, were associated with greater BMI, r = .40, p<.05, and heightened scores on the BES, r = .42, p < .05. Results indicate that for females with greater BMI and binge eating psychopathology, stress-induced eating may be a function of heightened desire to eat and negative affect rather than homeostatic hunger. Comfort food intake was not measured in the current study and thus further research is necessary to assess the influence of these subjective measures on stress-induced eating in obese and binge eating populations.

55. **Effect of DREADD-mediated inhibition of G-protein coupled signaling in lateral habenula neurons on operant cocaine or food self-administration and reinstatement in rats.** Sunila Nair, Denis Smirnov and John F. Neumaier. Department of Psychiatry and Behavioral Sciences, Harborview Medical Center, University of Washington, Seattle, WA 98104. The lateral habenula (LHb), part of the habenular complex in the dorsal diencephalon, is an important regulator of midbrain dopaminergic systems that are known to be involved in cocaine and food seeking behaviors. Here, we firstly examined the role of LHb neurons on operant cocaine and food self-administration. Rats were injected with a viral vector expressing a Gi/o-coupled DREADD (hM_4Di) in the LHb and trained to self-administer either cocaine (0.75 mg/kg/infusion) or 45 mg food pellets on a fixed ratio 1, 20 second timeout reinforcement schedule. Activation of hM_4Di by the pharmacologically inert synthetic ligand clozapine-N-oxide (CNO) [1 and 3 mg/kg] increased operant cocaine self-administration, but had no effect on food reinforced operant responding. Secondly, distinct cohorts of rats were trained to self-administer cocaine or food pellets and the operant response was extinguished over 10-14 days. Exposure to a single injection of cocaine (10 mg/kg, ip) or 5 pellets non-contingently at session start reinstated operant responding. CNO-induced increase in Gi/o-coupled signaling in LHb neurons, decreased cocaine-priming induced reinstatement, but had no effect on reinstatement of food seeking induced by a pellet prime. Finally, we examined the effect of LHb projection neurons to the ventral tegmental area on cocaine self-administration and cocaine-priming induced reinstatement. A Cre-recombinase dependent viral vector based flip-excision method was employed that involved injecting a combination of floxed, inverted hM_4Di into LHb neurons and a canine adenovirus 2 (CAV-2) engineered to express Cre recombinase into the VTA. CAV-2 efficiently infected VTA axon terminals and was retrogradely transported to the neuronal cell bodies in the LHb, resulting in the expression of hM_4Di receptors exclusively in LHb neurons that project to the VTA. CNO-induced activation of hM_4Di in LHb neurons projecting to the VTA had no effect on cocaine reinforced operant responding. In contrast, preliminary data indicate that this manipulation decreases cocaine-priming induced reinstatement of cocaine seeking. Taken together, these results suggest a differential role of activation of Gi/o-coupled signaling in LHb neurons on operant cocaine self-administration versus cocaine reinstatement. Further, LHb neurons projecting to the VTA possibly mediates cocaine-priming reinstatement but not operant cocaine self-administration in rats. This work was supported by NIH R21 DA034192 (S.N), and the Brain and Behavior Research Foundation NARSAD Young Investigator award (S.N).

56. **Role of nucleus accumbens core (NAc) in the modulation of motor vigor with mCPP: Implications for the quinpirole sensitization rat model of obsessive-compulsive disorder (OCD).** Mark C. Tucci, Anna Dvorkin-Gheva, Eric Johnson & Henry Szechtman. McMaster University. Research on the quinpirole sensitization rat model of OCD revealed that the behavioral phenotype of compulsive checking consists of three constitutive components, all greatly exaggerated by quinpirole: vigor of checking performance, focus on the task of checking, and satiety following a bout of checking. Moreover, there is good experimental evidence that the neuroanatomical site

mediating the vigor component includes the nucleus accumbens core (NAc) and that vigor can be altered pharmacologically with the serotonergic agonist mCPP. In the present study, we asked whether mCPP modulates vigor by acting on the NAc. The approach used examined whether effects of mCPP are altered by a lesion of the NAc substrate, with the expectation that if mCPP exerts its effects via NAc then those effects would be absent without NAc. **Methods:** Rats with sham or NMDA NAc lesion received saline or mCPP immediately before being placed into a large open-field for a 55-minute trial to measure checking behavior. **Results:** The effects of mCPP on one measure of motor vigor (frequency of checking) were eliminated by NAc lesion, but the effects on a second criterion measure of vigor (length of check) were not. **Conclusion**: mCPP modulates motor vigor through stimulation of serotonergic neurotransmission within and outside the NAc.

57. **Dose-dependent effects of amphetamine, atomoxetine and amantadine on cognitive outcome following traumatic brain injury in rats.** Frederick C.W. Lam[1], Cole Vonder Haar[1] & Catharine A. Winstanley[1]. [1]University of British Columbia. Traumatic brain injury (TBI) is a major problem affecting millions of people annually. However, despite many years of experimental research, all pharmaceutical treatments have failed. Additionally, there is a paucity of research exploring the chronic effects and chronic treatment of TBI in animals. In the current study, we trained rats on the five-choice serial reaction time task (5CSRT), a measure of visuospatial attention and impulsivity. Once rats reached baseline performance (~70 sessions), they were given a bilateral frontal brain injury via controlled cortical impact (Severe, Moderate, Mild or Sham). Following seven days recovery, rats were re-assessed for a post-injury baseline. Once the baseline had stabilized (20-25 days), a series of pharmacological challenges were assessed at different doses: amphetamine, atomoxetine and amantadine. Experimental and clinical literature have shown amphetamine and atomoxetine to be useful in reducing impulsivity and amantadine has been moderately successful at alleviating some cognitive deficits following TBI in humans. TBI resulted in significant impairments that were graded by injury severity on attention and impulsivity. Amphetamine treatment resulted in a dose-dependent increase in impulsive responses for all groups except the severe-injured animals who saw a significant reduction in impulsive responding. Amphetamine reduced accuracy in a dose-dependent manner for sham- and mild-injured animals, had no effect in moderate-injured animals and increased accuracy for severe-injured animals. Atomoxetine decreased impulsive responding across all groups in a dose-dependent fashion and increased accuracy across all groups at the low dose. Amantadine dose-dependently decreased impulsive responding across all groups, largely due to reductions in overall responding. Amantadine had no significant effect on accuracy. The results presented here highlight the need for more robust assessment of drugs used for treating impulse control disorders in the context of brain injury. Given the group by drug interaction observed with amphetamine, it is possible that other drugs may have differential effects dependent on the injury severity. Although there is considerable effort and interest, further testing is necessary to find an effective treatment that would ameliorate cognitive impairments for the very large population of TBI patients. Funded by the Canadian Institutes for Health Research.

58. **Neuroanatomical correlates of speech production in normal aging and mild Alzheimer's disease.** Rodríguez-Aranda, C.[1]; Waterloo K. [1,3] ; Johnsen, S.H. [3;] Eldevik, P [2]. Sparr, S.[4;] Wikran, G.C.[2], Herder M. [2] , Vangberg, T.R.[2.] [1]Dept. Psychology, University of Tromsø, Norway; and [2] Dept. Radiology,[3]Dept. Neurology; and [4] Dept. Geriatrics, University Hospital North Norway, Tromsø, Norway. *Background.* Increasing data show that verbal functions decline in early Alzheimer's disease (AD). For instance, verbal fluency (VF) impairments have long being recognized as a clinical feature of AD and are among the earliest manifestations the disease. Nevertheless, the neural underpinnings of this impairment are still unknown *Study objective.* The present study seeks to evaluate the neural

correlates of verbal accuracy and latencies for word generation in patients at the early stages of AD and age-matched healthy controls. *Subjects.* 18 mild AD patients and 24 healthy elderly. *Materials and procedures.* Semantic and phonemic verbal fluency tasks were evaluated. Presentation of the tasks was performed by using E-prime. The subject's speech was recorded during execution of verbal tasks and subsequently, spectrographic analyses were performed with CSL 4500 software. The quantified parameters were correct number of words and latencies of word generation. For brain imaging, we conducted measurements of cerebral gray matter (GM) and white matter (WM) using MRI techniques. Magnetic resonance scans were acquired on a 1.5 T scanner. T1 images were used for voxel-based morphometric analysis of the brain using the tools in the FSL program package. Linear regression analysis was performed between GM volume and speech scores. Furthermore, DTI was performed using 15 diffusion weighted directions (b = 1000 s/mm2), three repetitions. Fractional anisotropy (FA) and mean diffusivity (MD) maps were calculated from the DTI data and subjected to a tract-based spatial statistics (TBSS) analysis. Voxel-wise statistical regression between FA, MD and the target outcomes of the verbal tasks (correct words and intervals) were performed with a permutation-based inference method. *Results.* Although, AD patients had poorer VF scores than controls, the association between VF performance and structural brain measurements were mostly similar across groups suggesting a continuum in the association. However, one single association between semantic accuracy and GM volume in the putamen and superior and inferior colliculi clearly differentiated patients from controls. *Conclusions:* These findings demonstrate that VF impairments in AD patients are primarily associated with the same structural brain changes as in healthy elderly but at exaggerated levels. Notwithstanding, our data also indicate that specific VF deficiencies and their underlying neural correlates in AD are distinctive and do not merely correspond to accelerated aging.

59. **Effects of adenosinergic drugs on contextual fear conditioning, social interaction and locomotion in an animal model of schizophrenia.** Ramos A.C.[1]; Camerini B.A.[1]; Gouvêa D.A.[1,2]; Derci N.[1,2]; Vendramini, A.M.[1,2]; Suiama, M.A.[1,2]; Abílio V.C.[1,2]; Calzavara M.B.[1.] 1 Laboratório Interdisciplinar de Neurociência Clínica (LINC), Department of Psychiatry, UNIFESP. 2 Department of Pharmacology, UNIFESP. Clinical and neurobiological findings suggest that adenosinergic system could be implicated in schizophrenia. Adenosine A2a receptors (A2aR) are co-localized with dopamine D2 receptors (D2R) and form a functional heteromeric complex. The activation of A2aR decreases the affinity of D2R for dopamine, modulating the dopamine levels. This interaction could be implicated in schizophrenia patogenesis. The aim of this study is to evaluate the effects of 1) SCH58261, an antagonist, and 2) CGS21680, an agonist of A2a adenosine receptors, on emotional processing, through contextual fear conditioning (CFC), and negative and positive symptoms, through social interaction (SI) and locomotion measurement, in SHR, an animal model of schizophrenia, and Wistar rats (WR), in order to investigate the participation of adenosinergic transmission in the schizophrenia's pathophysiology. After treatment with different doses of SCH58261 or CGS21680, rats were submitted to CFC and SI, when the locomotion was also evaluated,. SHR presented CFC and SI deficits and hyperlocomotion, characterizing an animal model of schizophrenia. The treatment with SCH58261 didn't affect CFC, SI and locomotion in SHR and WR. Different doses of CGS21680 decreased CFC and locomotion; and enhanced time spending in SI in both strains. These results support an antipsychotic property of CGS21680 on symptoms-like behaviors in SHRs and Wistar.This work was supported by grants from 'from 'Fundação de Amparo à Pesquisa do Estado de São Paulo' (FAPESP – 2014/06961-5).

60. **Investigation of stressor controllability on anxiety-like behaviors in mice.** Kristin Rasmus Burrow[1], Jordan Hood[1], Steve Maier[1], Marissa Ehringer[1.] [1]University of Colorado Boulder. Stressful situations can lead to behavioral consequences such as anxiety, anhedonia, and increased drug-

seeking. However, behavioral control over a stressor has been shown to mitigate these stress-induced consequences in rats. In other words, uncontrollable stress produces behaviors in rats that resemble symptoms of depression and anxiety, while exactly equated controllable stress does not. This learned-helplessness phenomenon has been well characterized in the rat but not in the mouse. In rats, a well-characterized model involves exposing one group of animals to escapable shock (ES), in which rats have behavioral control over the termination of each of a series of tail-shocks by turning a wheel, while another group experiences inescapable shocks (IS) whose durations are yoked to those produced by the ES subjects, without control over terminating the tail-shocks. This exposure is followed by a number of behavioral tests that model anxiety and depression, to compare responses between the two groups. Here we conduct an original study on the effects of stressor controllability in mice. We employ the same ES/IS tail-shock paradigm used in rats, followed by three behavioral tests used to assess anxiety-like behaviors: the Open Field Test, the Social Interaction test and the Elevated Zero Maze. Our preliminary results suggest that IS mice show elevated anxiety/depression in the Open Field and Elevated Zero Maze models and an increase in aggressive behaviors during the Social Interaction Test, particularly in males. Broadly speaking, our results provide an important new mouse model to study stress-related disorders, where many genetic and genomics tools are more developed compared to the rat. In addition, we are interested in examining the effects of stress on later drug behaviors using this model.

61. **Intrahippocampal infusions of the extracellular matrix glycoprotein reelin ameliorates fear memory impairment associated with kindling of the basolateral amygdala.** Justin J Botterill[1], Daniel M Ferguson[1], Hector J Caruncho[2], Lisa E Kalynchuk[3]. 1 Department of Psychology, University of Saskatchewan, Saskatoon, Saskatchewan Canada. 2 College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan Canada. 3 Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada. Temporal lobe epilepsy is associated with a myriad of behavioral and cognitive comorbidities. In the present study, we used the kindling model of temporal lobe epilepsy to investigate these comorbidities from a preclinical perspective. Kindling refers to the gradual progression and intensification of elicited motor seizures resulting from repeated electrical stimulation of a discrete brain site. We have previously reported that 99 kindling stimulations of the basolateral amygdala (BLA) profoundly impairs hippocampal-dependent fear conditioning and reduces the number of hippocampal cells expressing the extracellular matrix protein reelin. Interestingly, reelin has significant effects on synaptic plasticity in the adult brain by enhancing the induction and maintenance of long-term potentiation, stimulating dendritic spine formation, and improving cognition through a NMDA receptor-dependent mechanism. In the present study, we were interested in determining whether acute intrahippocampal infusion of reelin could ameliorate the cognitive deficits associated with BLA-kindling on a hippocampal-dependent fear conditioning task. All rats received 99 electrical or control stimulations over the course of 6.5 weeks. Upon completion of kindling, a subset of BLA-kindled rats with a single cannula located in the ipsilateral dorsal hippocampus received a total of two intrahippocampal reelin infusions. All rats then underwent four days of fear conditioning, consisting of a 10 minute habituation session, a 7 tone-shock pairing training session, 4 training tones in a novel context, and a contextual memory test in the original training environment. The results of our study revealed no significant group differences during the habituation and training sessions, indicating that baseline behaviors and learning were comparable for all groups. However, during the novel context test, BLA-kindled rats engaged in significantly less conditioned freezing to training tones than control rats. Interestingly, BLA-kindled rats treated with reelin were not different than controls during this test. On the final testing day, all rats were returned to the original training environment to evaluate contextual memory of the training environment. BLA-kindled rats engaged in significantly less conditioned freezing to the training

environment and had fewer fecal boli in the operant chamber than controls. BLA-kindled rats that were treated with reelin displayed conditioned freezing and bolus counts comparable to controls. These results suggest that acute intrahippocampal infusion of reelin can restore cognitive deficits associated with kindling of the basolateral amygdala.

62. **Multigenerational Prenatal Stress Leads to Emotional Disturbances and Altered Neuroanatomical Pathology of the Medial Prefrontal Cortex (mPFC).** *Mirela Ambeskovic[1] , Erin A. Falkenberg[1], Bryan Kolb[1], Gerlinde A.S. Metz[1].* [1]Canadian Centre for Behavioural Neuroscience, University of Lethbridge, 4401 University Drive, Lethbridge, AB, Canada. Exposure to stress during pregnancy is a major risk factor for adulthood depression and anxiety. However, very little is known about the emotional and neuronal consequences of repeated maternal stress over many generations or multigenerational prenatal stress (MPS). Here we investigated: 1) the effects of MPS on depressive and anxiety-like behaviours, and neuroanatomical pathology of the mPFC; (2) possible sexually dimorphic effects of MPS on emotionality and neuroanatomy. Male F4 generation offspring were derived from a lineage in which their ancestral mothers (F0-F3) were stressed during pregnancy. Non-stressed controls were also tested. The male offspring was tested for depressive and anxiety-like behaviours at the age of 6 (young adults) months using a forced swim task (FST) and an elevated plus maze (EPM). Behavioural outcomes were related to spine density of the medial prefrontal cortex (mPFC or Cg3), a brain area centrally involved in depression and anxiety. The findings showed that MPS increased anxiety-like behaviours in females and decreased in males when compared to non-stressed animals. On contrary MPS increased depressive-like behaviours in male and did not affect female animals. Changes in the emotionality were related to neuroanatomical pathology of the mPFC. Male rats had higher spine density than females. Importantly, MPS reduced spine density of the Cg3 apical and basilar regions in both sexes. These findings suggest that MPS may contribute to adulthood mental illness and its associated symptoms such as depression and anxiety by compromising structural plasticity in the mPFC.

63. **Witness defeat: A novel animal model of vicarious stress-induced depression in female c57BL/6 mice.** Lace M. Riggs[1], Jason B. Alipio[1], Mirella A. Hernandez[1], Francisco J. Flores-Ramirez[1], Sergio D. Iñiguez[1]. [1]Department of Psychology, California State University, San Bernardino, CA, USA. Stress exposure is a prevailing risk factor for the development of mood-related illnesses, wherein women represent the greater majority of those who suffer from depression-, anxiety-, and posttraumatic stress- disorder. Despite the growing body of studies suggesting that affective disorders can arise after a traumatic event is vicariously experienced, this relationship remains to be examined in female subjects at the preclinical level. Thus, the objective of the current investigation is to examine whether the “witness defeat” paradigm – a model that dissociates emotional versus physical social stressors – induces a depression-like behavioral phenotype in female c57BL/6 mice. To do this, female mice witnessed the social defeat bout of a male conspecific, by a larger CD1 aggressor, for 10 consecutive days. Twenty-four hr after stress exposure, mice were tested in the social interaction, sucrose preference, tail suspension, forced swimming, and elevated plus-maze behavioral tests. As expected, the physically stressed male c57BL/6 mice displayed a depressive-like phenotype as inferred from decreases in social interaction, decreased sucrose preference, increased total immobility in the tail suspension and forced swim tests, along with increases in sensitivity to the anxiety-inducing environment of the elevated plus maze. Interestingly, when compared to non-stressed female controls, female mice exposed to witness defeat stress also displayed a depressive-like phenotype across the same behavioral assays. As such, our results indicate that exposing female c57BL/6 mice to the “witness defeat” paradigm may be used to examine the etiology of vicarious stress-induced mood-related disorders in female populations.

64. **Lipopolysaccharide-induced inflammation increases the expression, but not extinction, of conditioned fear.** Young MB[1], Howell LL[1,2]. [1]Emory University, [2]Yerkes National Primate Research Center. Mounting evidence from psychiatric research has revealed that the mind and the body are linked more intimately than previously appreciated. Psychological stressors can have profound effects on physiology, and traumatic or chronic physical ailments can engender deep psychological distress. However, appreciation is growing for the effects of more subtle immunological disturbances on psychological well-being and how these effects may contribute to psychiatric disorders. Among the best explored observations in this new field of research is the link between peripheral inflammation and depression, as some depressed populations react positively to anti-inflammatory treatments and higher indexes of psychological well-being are associated with reduced expression of pro-inflammatory genes. Less has been studied about how inflammation contributes to severe emotional trauma. Evidence in patients suffering from post-traumatic stress disorder (PSTD) suggests that inflammation may play a part in either its onset or its resistance to recovery through psychotherapy. To begin to explore the relationship between fear and inflammation, we administered a peripheral inflammatory stimulus (lipopolysaccharides; LPS) and measured its effect on the expression and extinction of conditioned cued fear. Administration of LPS before extinction training did not affect the amount of total fear observed during extinction or 48 hours later, when extinction was tested. However, animals treated with LPS exhibited significantly more fear during the first half of extinction training, suggesting that inflammation may increase fear in certain populations, such as those suffering from PTSD. Subsequent studies sought to characterize the physiological and signaling mechanisms underlying this effect, revealing a novel mechanism though which the expression of fear is modulated. This research funded by NIH/NIGMS K12 GM000680.

65. **Long-term ovariectomy increases vulnerability to chronic stress and modulates the effects of fluoxetine on hippocampal plasticity.** Mahmoud R[1,2], Wainwright SR[1,2], Chaiton JA[1], Lieblich SE[1], Galea LAM[1,3]. [1] University of British Columbia. [2] Program in Neuroscience. [3] Department of Psychology. Women are twice more likely than men to suffer from depression, and sex differences are evident in antidepressant efficacy. These findings suggest a role of gonadal hormones in the development of depression and in antidepressant efficacy. Despite this, male animals are almost exclusively used in preclinical depression research, hindering our full understanding of the disease pathoetiology and the mechanisms underlying antidepressant efficacy. The purpose of this study was to test the effect of long-term hypogonadism on the development of depressive-like phenotypes and on antidepressant efficacy in middle-aged female Spague-Dawley rats. We exposed ovariectomized (OVX) and sham-operated rats to 6-weeks of chronic unpredictable stress (CUS); a protocol commonly used to induce depressive-like phenotypes in rodents. At the start of week 4, rats received chronic daily injections of a sub-threshold dose of fluoxetine (FLX) or vehicle. All rats were assessed on tasks that measure depression- and anxiety-like behaviour. OVX rats displayed more passive and less active behaviour than sham-operated rats in the forced swim test, and had a higher latency to feed in the novelty suppressed feeding task. Interestingly, regardless of ovarian hormone status, fluoxetine treatment did not attenuate anxiety- or depression-like behaviour. However, despite the lack of behavioural efficacy, fluoxetine treatment was associated with significant neuroplastic changes in the hippocampus (cell proliferation and survival), and this effect was dependent on ovarian hormone status. Furthermore, in the dexamethasone suppression test to assess hypothalamic-pituitary-adrenal axis function, OVX rats showed higher post-stress corticosterone peak. Our findings show that ovarian hormones protect females from the deleterious effects of chronic unpredictable stress, but do not enhance the efficacy of sub-threshold fluoxetine treatment.

66. **Chronic Minocycline Treatment Rescues Social Behavioral Deficit in Male Fmr1 KO mice.** Suk-Yu Yau [1], Christine Chiu [2], Mariana Vetrici [1], Brian R. Christie [1, 1]Division of Medical Sciences, University of Victoria, Victoria, BC, Canada; [2]Department of Biology, University of Victoria, Victoria, B.C., Canada. Fragile X syndrome (FXS) is the most common form of inherited intellectual disability. It is caused by a mutation of *Fmr1* gene which leads to loss of its gene product, Fragile X Mental Retardation Protein. Minocycline is a tetracycline antibiotic which has been used as an effective treatment in clinical trials of FXS patients. We examined if chronic minocycline treatment could rescue the behavioral deficit in social interaction in the *Fmr1* knockout mice. Minocycline was administered in drinking water to the newborn mice until they reached two months of age, followed by sociability and social preference tests. In the three chamber test, the test mice were introduced to a restrained stimulus mouse (S1) for 10 min to assess sociability, followed by introduction of a second restrained stimulus mouse (S2) for 10 min to assess social preference. Neither *Fmr1* knockout nor minocycline treatment affects performance in sociability test. However, Fmr1 knockout significantly decreased social preference to S2 mice as indicated by decreased exploration ratio to the S2 mice. Conversely, minocycline treatment effectively increased exploration ratio to the S2 mice in *Fmr1* knockout mice, but show no effect in their wildtype littermates. The findings suggest that minocycline treatment improves behavioral deficit in social interaction seen in FXS.

67. **Targeted GABA(A) pharmacotherapy in a mouse model of Fragile X Syndrome.** Schaefer, Tori L; Ashworth, Amy A; Davenport, Matthew H; Stegman, Melinda S; Erickson, Craig A; Division of Child and Adolescent Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229 USA. Fragile X Syndrome (FXS) is the most common inherited form of developmental disability (DD) and affects 1 in 4,000 persons. FXS is responsible for up to 2-6% of all cases of DD and is a prevalent single gene cause of autism spectrum disorder. FXS is caused by an expanded CGG triplet repeat expansion resulting in methylation and transcriptional silencing of the Fragile X Mental Retardation 1 gene (*FMR1*) and subsequent deficient production of Fragile X Mental Retardation Protein (FMRP). FMRP is a known RNA binding protein responsible for translational control of hundreds of mRNAs involved in intracellular and synaptic signaling and plasticity. Behavioral dysfunction in FXS is associated with an imbalance in excitatory/inhibitory signaling. Excessive signaling via the excitatory mGlur5 receptor has been extensively characterized although clinical efforts to reduce excitatory neurotransmission and improve behavior with mGlur5 receptor antagonists have failed. Inhibitory signaling including phasic and tonic inhibition in the *Fmr1* knock out (KO) mouse model of FXS is drastically reduced in brain regions important for emotional, fear, and cognitive processing. The gamma-aminobutyric acid receptor A (GABA(A)) mediates inhibitory control and several subunits are regulated by FMRP and are reduced in the amygdala, hippocampus, and cortex of *Fmr1* KO mice. This suggests GABA(A) pharmacotherapy may be a viable treatment mechanism for FXS. Non-specific positive modulation of GABA(A) using traditional benzodiazepines is not suitable for long-term pharmacotherapy in individuals with FXS due to sedating and cognitive dulling effects via modulation at α1 and α5 receptor subunits, respectively. For this reason, selective modulation of GABA(A) containing α2 or α3 subunits have been studied in *Fmr1* KO mice using a novel drug, AZD7325 (partial agonist at GABA(A) α2,3 subunits). Acute drug treatment in juvenile *Fmr1* KO mice greatly attenuated seizure susceptibility during an audiogenic seizure paradigm. In adult mice, chronic treatment with AZD7325 dose dependently resulted in improved memory, attenuated acoustic sensory reactivity and reduced fear behavior. Coordinated modulation of the immediate early gene, extracellular signal-regulated kinase (ERK1/2), is altered in the hippocampus and amygdala of *Fmr1* KO mice and is critical for memory and appropriate behavior in response to sensory stimuli. Modulation of ERK1/2 in *Fmr1* KO mice treated with AZD7325 may be important for

the behavioral effects observed in these mice. Funded by the FRAXA Research Foundation and the National Fragile X Foundation.

68. **Neonatal (+)-methamphetamine exposure impairs egocentric learning in the Cincinnati water maze (CWM) and working memory in the radial water maze (RWM) in rats.** Sarah A. Jablonski, Arnold Gutierrez, Trisha M. Tee, Kathryn L. Suttling, Michael T. Williams & Charles V. Vorhees. Division of Neurology, Department of Pediatrics, Cincinnati Children's Research Foundation. Rat pups treated with (+)-methamphetamine (MA) on postnatal days (P)6-15 exhibit long-term egocentric route-based learning deficits in the Cincinnati multiple-T water maze (CWM; e.g., Vorhees et al., 2009). Similar impairments in allocentric working memory following developmental MA exposure are not known. Pre-treatment with the spin-trapping agent, N-tert-butyl-α-phenylnitrone (PBN), prevents adult MA-induced dopamine neurotoxicity (Cappon et al., 1996). The objectives of the present experiment were to (1) examine the effects of P6-15 MA (10 mg/kg x 4/day at 2-h intervals) on egocentric and allocentric learning in both young and adult rats and (2) determine whether reactive oxygen species (ROS) generation is a determinant of long-term behavioral deficits induced by MA by pretreating animals with PBN (40 mg/kg). A split-litter design was used with one male/female pair per litter receiving one of four treatments (PBN/MA; Saline/MA; PBN/Saline; Saline/Saline, administered s.c.). Each PBN or saline injection occurred 30-min prior to each MA or saline injection. For behavioral testing beginning on P30 (males), the CWM was truncated and a reduced number of testing days was used, compared with animals tested as adults (females). Regardless of pre-treatment, MA-exposed rats showed a significant increase in CWM errors compared with controls. There was no main effect of PBN or interaction of MA x PBN. As adults, MA-exposed rats showed significant increases in errors and latency to reach the platform compared with controls, however there was no main effect of PBN or interaction of MA x PBN. Rats also underwent the working/reference memory version of radial water maze (RWM). MA-exposed males exhibited a significant increase in reference, working memory, and total errors compared with controls, but there was no effect of PBN or interaction of PBN x MA. MA-exposed females showed a significant increase in reference errors, but there was no effect of PBN or interaction of PBN x MA. Taken together, these findings demonstrate that neonatal treatment with MA induces cognitive impairments that emerge early and affect allocentric working and reference memory and egocentric learning. For the data analyzed so far, the ROS spin-trapping agent PBN was ineffective at attenuating the cognitive deficits induced by early MA exposure. (Supported by T32 ES007051).

69. **Limbic neuropeptide y-1 receptors modulate vulnerability to social and metabolic challenges depending upon gender and maternal care.** Palanza P.[1] , Paterlini S[1], Panelli R[1], Gioiosa L[1], Parmigiani S[1], Mele P[2], Longo A[2], Eva C[2]. [1]Dept. of Neuroscience, University of Parma, Parma, Italy; [2]NICO, Neurosci. Inst. of the Cavalieri Ottolenghi Fndn, Univ. of Torino, Torino, Italy. Interaction between genes, sex, early developmental events and stress plays a crucial role in the development of psychological and metabolic disorders. Neuropeptide Y (NPY) and its receptors have been shown to be involved in individual vulnerability to stress, anxiety, depression and metabolic disorders. We have demonstrated that conditional knockout Npy1r/rfb mice, in which the inactivation of the Npy1r gene was restricted to excitatory neurons of the forebrain in juvenile and adult mice, showed lower body weight growth, increased anxiety and CRH-IR in the PVN in relation to sex and the maternal cares received during the first postnatal week (Bertocchi et al. 2011). We examined social behavior, body weight growth in response to hyperchaloric diet and respone to social stress in mutant and control mice. To remove Dox-induced inhibition of gene inactivation, after birth (PND0), Npy1r/rfb and their control littermates (Npy1r/2lox) were fostered to lactating mice displaying high (HM- FVB/J and CD1 strain) or low (LM - C57BL/6J) maternal care. During postnatal development, between PND 45 and

100, after conditional Cre-mediated inactivation of the limbic Npy1r gene is induced, Npy1r/rfb male, but not female, mice showed a slower body weight growth compared to controls. Mice were then exposed to either standard diet (STD) or high fat diet (HFD) for 3 weeks. Starting from the second day of HFD, conditional mutant males that were reared by HM foster dams showed a rapid body weight increase that persisted throughout the HFD regimen; no differences were observed in females. While the overall amount of food consumed did not differ from their control littermates, Npy1r/rfb male mice showed higher Kcal intake during the first week of HFD. Npy1r/rfb mutant males exposed to HFD also showed higher levels of the glucose curve in the glucose tolerance test (GTT) and higher perigonadic white adipose tissue as compared to controls and STD mice. These effects were enhanced when male conditional mutants and their control littermates were fed with HFD after been exposed to a chronic psychosocial stress procedure. These results indicate that low limbic NPY1R expression induced by conditional gene inactivation increases susceptibility to hyperchaloric diet and stress in adulthood, and can mediate vulnerability to metabolic disorders in a sex-dependent manner. Also, the early maternal environment affect NPY1R expression in the limbic system, as few or no effects of gene inactivaction were observed in mice reared by LM foster mothers. **Support:** PRIN2008 PLKP3E_002; PRIN 2010 7MSMA4_005.

70. **The role of pituitary adenylyl cyclase activating polypeptide in nicotine-induced aversion in C57/BL6 mice.** Prableen Singh, Andy Tseng, Abdul Hamid, Paul Marquez and Kabirullah Lutfy. Department of Pharmaceutical Sciences, College of Pharmacy, Western University of health Sciences, Pomona, California, USA. Nicotine addiction is a major public health and socioeconomic issue. The negative affective symptoms associated with intake of high doses of nicotine or following nicotine withdrawal are known to respectively hinder or facilitate nicotine's continued use. Thus, the present study was designed to determine the role of endogenous pituitary adenylyl cyclase activating polypeptide (PACAP) in motivational and reinforcing effects of nicotine, known to play a critical role in the initiation and maintenance of nicotine addiction. We used place conditioning and two-bottle choice (TBC) paradigms to assess the role of PACAP in motivational and reinforcing effects of nicotine, respectively. In the TBC paradigm, PACAP heterozygous and wild-type mice were housed individually while they had access to two water bottles for a week. Mice were then given a choice between water versus nicotine (20µg/mL) for the following week. The concentration of nicotine was increased two-fold on each subsequent week. Our results revealed that mice lacking PACPA consumed more nicotine compared to wild-type mice at the two higher concentration of nicotine (40 and 80µg/mL). In the place conditioning paradigm, mice lacking PACAP and their wild-type littermates/controls were tested for basal place preference toward the conditioning chambers on day 1. Mice were then injected with either saline or nicotine (1 mg/kg) and confined to either vehicle-paired chamber (VPCh) or drug-paired chamber (DPCh), respectively. In the afternoon, animals received the alternate treatment and were confined in the opposite chamber for 15 min. This twice daily conditioning lasted for 8 days. Mice were then tested for postconditioning place preference on day 10. On each test day, mice were placed in the neutral chamber and allowed to explore all the three CPP chambers and the amount of time that mice spent in each chamber was recorded. Our results showed that wild-type mice spent significantly lesser amount of time in the nicotine-paired chamber (DPCh) compared to saline-paired chamber (VPCh), showing that these mice exhibited aversion following nicotine administration. However, this response was blunted in mice lacking PACAP, showing that these mice failed to exhibit a robust aversive response following the same conditioning paradigm. Together, the current results suggest that endogenous PACAP may mediate the aversive effects of nicotine and PACAP and its receptors may be a novel target for the development of nicotine addiction and smoking cessation.

71. **The role of pituitary adenylyl cyclase activating polypeptide in nicotine-induced aversion in C57/BL6 mice.** Singh, Prableen; Tseng, Andy; Hamid, Abdu; Marquez, Paul; Lutfy, Kabirullah. The neuropeptide oxytocin has been implicated as a key modulator of complex physiological and behavioral functions. In particular, its role in affiliative behaviors has gained attention and clinical trials are ongoing to determine the efficacy of oxytocin as a treatment for autism. Previous preclinical studies have been very informative, but direct manipulation of oxytocin in the brain has been a challenge due to its poor brain penetrance and similar affinity for both oxytocin and vasopressin receptors. To circumvent these problems we have developed a method to stimulate or inhibit endogenous central release of oxytocin. By utilizing recently available knock-in mice that express Cre recombinase (Cre) under the control of the endogenous oxytocin promoter we have been able to selectively express Cre-dependent Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in oxytocin neurons in the PVN. DREADDs are G protein-coupled receptors that are quiescent unless activated by an otherwise inert synthetic agonist (clozapine-N-oxide, CNO). Therefore, peripheral injection of CNO can transiently stimulate (hM3Dq) or inhibit (hM4Di) DREADD-expressing neurons in awake and behaving animals. Localized expression of DREADDs in oxytocin neurons was confirmed via immunofluorescence. The ability of CNO to stimulate these neurons was determined by *in vivo* microdialysis with LC-MS detection for central oxytocin release and c-Fos double labeling of oxytocin neurons to indicate neuronal activation. Mice receiving CNO were tested on a variety of behavioral measures to determine if there were any overt behavioral effects of increased or decreased oxytocin release. Lastly we tested whether inhibition of oxytocin neurons would attenuate the prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy). MDMA has robust prosocial effects across species and there is some evidence to suggest that increased oxytocin release is necessary for these effects. Together these studies validate a new method for non-invasive control of endogenous oxytocin neurons and highlight the behavioral effects of both activating and inhibiting these neurons.

72. **Taurine modulates the effects of ethanol on zebrafish exploratory behavior.** Blaser, R.E.,[1] Rosemberg, Denis B.,[2] Braga, Marcos M.[2, 1]Department of Psychological Sciences, University of San Diego, San Diego, CA, USA [2]Programa de Pós-graduação em Bioquímica, Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil. Taurine is an amino acid that may be important in a variety of CNS functions including homeostasis, inhibitory signaling, and modulation of the glutamatergic system. In particular, taurine may prevent excitotoxicity and oxidative stress, which could allow it to act as a preventative for some of the detrimental effects of ethanol exposure. A substantial body of research now exists on zebrafish as a model organism for the study of alcohol abuse, and it has recently been demonstrated that taurine may counteract some of the behavioral effects of ethanol in zebrafish. In a previous study, taurine appeared to differentially affect the locomotor and the anxiolytic effects of ethanol on fish. The current experiment was designed to further investigate this effect, using a different behavioral test, the split-depth tank. In the absence of ethanol, the effects of taurine were generally U-shaped, although only the highest dose (400 mg/L) produced a significant effect on most behaviors. Lower doses of taurine were sufficient to counteract the effects of 1.0% ethanol on both general locomotor and anxiety-related measures in this test.

73. **Adult zebrafish and conditioned place preference as a model of drug reward.** Adam D. Collier[1], Natalie R. Lodinger[1], Kanza M. Khan[1], Erika M. Caramillo[1], and David J. Echevarria[1, 1]The University of Southern Mississippi. Addiction and substance abuse amass hundreds of billions of dollars annually in costs associated with healthcare, crime and lost productivity, solely within the United States. The most commonly used substances are sanctioned throughout much of the world (e.g.,

alcohol, nicotine and caffeine), the use and abuse of which may result in psychological and/or physiological dependence. Efficacious treatments for substance use disorders remain few in number. A better understanding of environmental, genetic, pharmacological and neurobiological mechanisms implicated in the pathogenesis of addiction will facilitate treatment development and aid in the identification of targets for therapeutic intervention. Animal models such as the zebrafish (Danio rerio) have gained momentum within various domains of translational research, and as a model of complex brain disorders (e.g., addiction). The evolutionarily conserved nature of drug abuse behavioral phenotypes and the functional homology of neural pathways (e.g., dopamine) in the zebrafish brain, in addition to shared genes related to addiction in humans, establish the zebrafish as a powerful *in vivo* model of drug abuse. The conditioned place preference (CPP) was employed in the present study to evaluate the rewarding properties of alcohol, nicotine and caffeine in adult zebrafish. Zebrafish were first allowed to explore an apparatus divided into two visually discriminative environments, and the initial preference to spend time in each environment was measured. On the following day, zebrafish were then conditioned with a dosage of drug via immersion in their least preferred side over a number of conditioning sessions. During the final day of testing, zebrafish were once again allowed to explore the entire apparatus and were probed once again for their preference to spend time in each environment. The current study reports CPP behavior in adult zebrafish following acute (1 day) or chronic (7 days) exposure to alcohol (0.0%, 0.25%, 0.50% or 1.00% vol/vol), caffeine (0 mg/l, 50 mg/l, 100 mg/l and 150 mg/l) and nicotine (0mg/L, 2.5 mg/l, 5 mg/l and 10 mg/l).

74. **THC decreases cognitive effort without impairing attentional processes: The role of the cannabinoid system in a distinct form of cost/benefit decision-making.** Mason M. Silveira (1). Wendy K. Adams, Catharine A. Winstanley. Department of Psychology, University of British Columbia, Canada. Cannabis is the most commonly used illicit substance worldwide, with a purported 10% of the Canadian population using the drug in the past year alone. The increasing popularity of cannabis is likely a consequence of growing societal acceptance around its use both recreationally and medically. However, the drug is linked to a number of adverse cognitive and psychosocial impairments, and longitudinal studies indicate that cannabis use is associated with less educational attainment, less work commitment, and higher rates of welfare dependence. These prospects may reflect a fundamental impairment in effortful cost/benefit decision making, whereby cannabis impairs the willingness to expend the greater cognitive effort associated with advantageous outcomes. To establish a causal role of cannabinoid signaling in such cost/benefit decision-making, we evaluated the effects of various cannabinoid drugs on the rat Cognitive Effort Task (rCET). In this task rats must choose between two options differing in reward magnitude (two pellets versus 4 pellets) but also in the amount of cognitive effort required to obtain these rewards (easy (1s) versus hard (0.2s) visuospatial discriminations, respectively). Thirty-two Long-Evans rats were trained on the task and administered the following drugs: rimonabant, a CB_1 receptor antagonist; AM 630, a CB_2 receptor antagonist; URB597, a FAAH inhibitor which prevents the breakdown of the endogenous cannabinoid anandamide; Δ-9 tetrahydrocannabinol (THC), the main psychoactive component of cannabis; and cannabidiol, a phytocannabinoid linked to the purported therapeutic effects of cannabis. These drugs affected a variety of behavioural measures, but only THC affected decision making. Specifically, THC decreased cognitive effort at all doses tested, thereby making rats less willing to initiate hard attentional trials associated with larger reward. Importantly, this decrease in effortful choice was observed across rat groups differing in baseline choice performance (termed “workers” and “slackers”), and cannot be attributed to impaired cognitive ability, as THC leaves attentional faculties intact. Data relating the THC effect to CB_1 receptor expression levels in prefrontal and limbic structures will also be presented. This investigation is the first of its kind to implicate the cannabinoid

system in effortful cost/benefit decision-making, and suggests that impaired decision-making processes may underlie the adverse psychosocial outcomes associated with cannabis use.

75. **Baseline poor-decision making on a rat gambling task is exacerbated following cocaine self-administration and incubation of craving: investigating individual vulnerability to addiction.** Ferland, Jacqueline-Marie N[1]. & Winstanley, Catharine A[1]. [1]University of British Columbia.
Drug addiction is a widespread psychiatric disorder that is defined by a cycle of drug seeking, repeated attempts to quit, and relapse. Maladaptive decision-making is commonly found amongst substance abusers and is thought to play an integral role in the development and maintenance of addiction. Indeed, human studies using the Iowa Gambling Task (IGT), a validated measure of decision-making, have found that substance dependent individuals tend to choose the least advantageous option (associated with less reward over the course of the task) and are less likely to change their strategy following losses compared to controls. These deficits have been found to worsen following withdrawal. Animal studies using self-administration have found that cocaine use impairs a variety of executive functions including reversal learning and impulse control. However, no preclinical work has examined whether cocaine self-administration or prolonged withdrawal has an impact on cost/benefit decision-making. More critically, no animal models have focused on individual differences in decision-making, which may underlie the likelihood to abuse drugs and relapse. To investigate this relationship, we trained 24 male Long-Evans rats on the Rat Gambling Task (rGT), a rodent analogue of the IGT. In brief, animals were allowed to choose between 4 different nosepoke holes of an operant box, each associated with a different sugar pellet reward (1-4 pellets), penalty time out (5-40s), and probability of receiving a reward over a penalty (0.9-0.4). The advantageous options (those resulting in 1 or 2 sugar pellets) are commonly chosen while the disadvantageous options (3 and 4 sugar pellets) are often avoided. As in the IGT, the goal of the task is to maximize the amount of reward received within a 30-minute session. Once behavioural stability was reached, rats were implanted with jugular vein catheters and were allowed to self-administer cocaine for 10 days followed by 30 days of withdrawal. Decision-making was simultaneously measured by rGT performance throughout the experiment. Results indicated that a subgroup of animals with baseline preferences for the disadvantageous options self-administered greater amounts of cocaine and performed worse (i.e. chose the risky options more) following self-administration. Furthermore, 30 days of withdrawal exacerbated these deficits. These data demonstrate that cocaine self-administration and withdrawal intensifies poor decision-making within a vulnerable subgroup, providing a model by which we can begin to investigate the individual susceptibility to abuse drugs and relapse.

76. **Injections of DHβE into the anterior nucleus accumbens or the ventral tegmental area reduce nicotine-induced enhancement of responding for a conditioned reinforce.** Rayane I. Tabbara[1, 2], Paul J. Fletcher[1, 2, 3]. [1]Department of Psychology, University of Toronto; [2]Section of Biopsychology, Centre for Addiction and Mental Health; [3]Department of Psychiatry, University of Toronto.
Environmental stimuli associated with the pharmacological effects of nicotine promote tobacco use and dependence. Evidence from animal models suggests that nicotine enhances the motivational properties of conditioned stimuli (CSs) previously paired with reward, such that rodents respond more for presentations of these stimuli. This enhanced responding implies that these CSs have acquired conditioned reinforcing properties. The present experiments examined neuropharmacological processes by which nicotine enhances responding for a conditioned reinforcer (CRf). Male Long-Evans rats were implanted with a bilateral guide cannula aimed at the anterior nucleus accumbens (NAc) or the ventral tegmental area (VTA). Next, thirsty rats received a nicotine injection (0.4 mg/kg) prior to 12 sessions of Pavlovian conditioning. Each session consisted of 30 trials in which a 5-sec

tone-light CS was paired with 0.05 ml of water. Tests for conditioned reinforcement were then conducted during which presses on a 'CR' lever produced the CS without the US, whereas presses on an 'NCR' lever had no consequences. Each rat was tested under the following conditions: in the SAL/SAL condition, rats received a saline infusion into the targeted brain region and a saline injection prior to test; in the SAL/NIC condition, they received a saline infusion and a nicotine injection (0.2 mg/kg); in the DHβE/SAL condition, they received an infusion of the $\alpha_4\beta_2$ nicotinic antagonist dihydro-β-erythroidine (DHβE; 10 nmol) and a saline injection; in the DHβE/NIC condition, they received an infusion of DHβE and a nicotine injection. Nicotine enhanced responding for a CRf and rats in the NIC/SAL condition made more responses on the CR lever relative to those in the SAL/SAL condition. In the anterior NAc and the VTA, DHβE reduced the nicotine-induced enhancement of responding for a CRf. Thus, rats in the DHβE/NIC condition responded fewer times for a CRf relative to those in the SAL/NIC condition. DHβE blocked nicotine's enhancing effects on responding for a CRf at a greater magnitude when infused into the VTA compared to when infused into the anterior NAc. These preliminary results demonstrate that pharmacological blockade of $\alpha_4\beta_2$ nicotinic acetylcholine receptors in the anterior NAc and the VTA diminish nicotine's enhancement of the motivating properties of reward-paired CSs.

77. **Sex and age differences in alcohol drinking behavior in socialized vs isolated C57BL/6J mice.** O. Evans, P. Currie, R. Pastor. Department of Psychology, Reed College, Portland, OR. The effect of developmental environment in later life alcohol drinking behavior has been relatively unexplored using traditional animal models. This study was designed to examine how socialization would influence alcohol consumption in mice at different stages of development. Male and female C57BL/6J mice were introduced to specialized housing conditions at adolescence (4 weeks post birth) and adulthood (7 weeks post birth). Isolated mice were single housed in plain mouse cages, while socialized mice were housed in pairs, and given access to various types of environmental enrichment. After habituating to the housing conditions, we implemented a modified binge-like drinking in the dark (DID) test, allowing two-hour free access daily to increasing concentrations of ethanol solution (10%, 20% and 30%; 4 days per concentration). Plexiglas clear perforated cage dividers were introduced (for two hrs) to allow for individual measures of intake (cage space was then divided in two halves). Dividers were also introduced for single-housed animals to control for the reduction in space available during the drinking test. Mice drank pharmacologically relevant amounts of ethanol that increased with concentration, ranging from 2.0 to 4.0 g/kg. An overall age effect was found, with adolescent mice drinking more ethanol across concentrations. Neither sex nor housing condition (socialization vs. isolation) modified ethanol drinking per se. However, a more detailed analysis showed significantly higher ethanol consumption in adolescent females. Additionally, socialized adolescent females consumed significantly more ethanol than every other group examined in the study. These findings reinforce the important influence of sex and age over behavioral adaptation following alcohol exposure, and raise important questions about the influence of developmental environment on ethanol drinking behavior. Importantly, however, these effects were not seen to be specific for ethanol, as the same pattern of sex, age, and housing effects were found for water and sucrose intake.

78. **Voluntary consumption of a sweetened alcohol solution is increased by adolescent social isolation via an altered circadian drinking phenotype.** Jules B. Panksepp[1], Andrey E. Ryabinin[1,2.] [1] Department of Behavioral Neuroscience [2] Portland Alcohol Research Center, Oregon Health and Science University. 'Alcopops' collectively refer to a group of heavily sweetened alcoholic beverages designed primarily for consumption by young people. The vast prevalence of these hedonically flavored solutions can be problematic during adolescence, as they supply concurrent rewards (i.e.,

intoxication and palatable tastants) to the developing adolescent brain, which may then promote additional intake. Furthermore, it is well known that the presence or absence of social peers can influence ethanol (EtOH) intake patterns. Using an ascending concentration 2-bottle choice procedure, we evaluated 24-h patterns of voluntary consumption of EtOH solutions that were 'masked' with the sweetener saccharine (Sac) in adolescent mice that had been weaned into social isolation or housed together in same-sex pairs. Isolated (ISO) mice from 4 genetic backgrounds (BALB/cJ, C57BL6/J, FVB/NJ, MSM/msJ) consumed substantially more EtOH compared to socially housed (SOC) mice, which was unexpected given the substantial genetic differences between these strains in laboratory tests of adolescent social motivation. ISO mice continued to consume more when bottles were switched to EtOH-only, an effect that was stronger in females. Prior to EtOH+Sac introduction, mice from all strains exhibited modest levels of polydipsia, and independent sampling groups demonstrated that many of the ISO mice also drank more Sac-only. Effect sizes were nevertheless highest for EtOH+Sac and EtOH-only, suggesting that ISO mice modulate their enhanced intake according to reward salience (e.g., EtOH intoxication and pleasurable tastants). Of the 256 mice that were assessed, average blood [ethanol] was >90mg/dl, indicating intoxication in many individuals. Surprisingly, blood [ethanol] 4 h into the dark phase was not different between any groups of ISO vs. SOC mice despite overall differences in 24-h intake. Lickometer studies reproduced the 'isolation' effect in FVB mice and revealed a late-phase bout of EtOH+Sac drinking that occurs in ISO, which was also accompanied by higher blood [ethanol]. Overall, our findings illustrate that ISO mice voluntarily consume more EtOH than their SOC counterparts independent of genetically based differences in sociability. Moreover, circadian analysis demonstrates that this phenotype is due to ISO mice drinking at times when SOC mice do not. Funding: NIAAA (R01AA019793), NIMH (F32MH096475).

79. **Characterizing responses to a *de novo* alcohol-associated cue in healthy social drinkers.** Leah M. Mayo & Harriet de Wit. University of Chicago Department of Psychiatry & Behavioral Neuroscience. It is well-established that drug-related cues can elicit a variety of responses, including enhanced self-reported craving, changes in affect, and a bias in attention, even in the absence of drug. However, little information exists regarding the acquisition of these responses in humans. Previously, we created a novel conditioning paradigm (Mayo et al., 2013) and demonstrated that healthy, non-dependent humans will elicit conditioned responses to a methamphetamine-associated contextual following conditioning (Mayo & de Wit, 2015). Here, we aim to use this same paradigm to determine whether similar conditioning will occur with a different drug: alcohol. Healthy adult social drinkers (N = 36) came into the lab for 6 sessions: a pre-test session, 4 conditioning sessions, and a post-test session. At the pre-test, we assessed baseline responses to two audio-visual study cues. Responses include behavioral preference, emotional reactivity (assessed via facial electromyography of the corrugator and zygomatic muscles) and attentional bias (measured using electrooculography during a modified visual probe task). Participants then came in for 4 conditioning sessions; 2 each with alcohol (0.6g/kg everclear with either cranberry or orange juice) and placebo (1% everclear solution with juice), administered under double-blind conditions in alternating order. During alcohol sessions, one audio-visual cue was presented on a computer screen for 30min during peak drug effect; the other audio-visual cue was presented during placebo sessions. Following the conditioning sessions, participants completed a post-test session similar to the first session, in which we assessed behavioral preference, emotional reactivity, and attentional bias towards the cues. Following conditioning, participants demonstrated enhanced attention towards the alcohol-paired cue, as indicated by an increase in initial orienting. In addition, subjective responses to alcohol predicted change in attention, such that those who reported "liking" the effects of alcohol more demonstrated a greater increase in initial orienting. This study not only demonstrates *de novo* conditioning in human

subjects, but also highlights important differences between conditioning with alcohol and stimulant drugs.

80. **Enhanced sensitivity to cocaine increases perineuronal net staining in the adult medial prefrontal cortex.** Megan Slaker[1], Barbara A. Sorg[1]. [1]Washington State University, Vancouver. Perineuronal nets (PNNs) are unique structures of extracellular matrix within the central nervous system. They surround the soma and proximal dendrites of parvalbumin-containing neurons within the medial prefrontal cortex. The appearance of PNNs during development coincides with the closure of critical periods, during which time external stimuli influence development of neuronal circuits. Cocaine is a psychomotor stimulant that increases movement in rats; after repeated cocaine exposure, rats become sensitized to cocaine and display an enhanced locomotor response. We sought to determine the effect of cocaine exposure on PNNs within the medial prefrontal cortex. We hypothesized that exposure to a strong external stimulus (cocaine) during adulthood would increase the intensity of PNNs within multiple regions of the prefrontal cortex. To test this, we exposed adult, male rats to 1 or 5 days of cocaine (15 mg/kg, i.p.) and locomotor activity was measured each day to assess sensitization. Two hours or 24 hr following the last injection, rats were sacrificed and the prefrontal cortex was assessed for PNN intensity. Preliminary results suggest that 2 hr following the last cocaine injection, PNN intensity was increased in the prelimbic region of the prefrontal cortex, but was unaffected in the infralimbic or orbitofrontal regions. This increased intensity was positively correlated with sensitized locomotor activity, suggesting that PNN intensity in the prelimbic region may serve as a functional read-out of cocaine-induced motivational behavior. In contrast to the increase at 2 hr, at 24 hr following the last injection, no differences were observed in intensity in any brain region between cocaine and saline-treated rats. These results demonstrate that exposure to cocaine increases PNN intensity within the prefrontal cortex and suggest that repeated cocaine may render the medial prefrontal cortex resistant to normal physiological stimuli. Funding: NIH DA 033404.

81. **The role of endogenous nociceptin in anxiety-like behaviors in C57/BL6 mice.** [1]Perez, Sidney; Marquez, Paul[2]; Hamid, Abdul[2]; Lutfy, Kabirullah[2]. [1]California State Polytechnic University, Pomona, California, USA; [2]College of Pharmacy, Western University of Health Sciences, Pomona, California, USA. Orphanin FQ/nociceptin, the endogenous ligand of the opioid receptor-like (ORL1, also known as NOP) receptor, has been shown to regulate anxiety-like behaviors in rodents. Low doses of the peptide reduce anxiety but higher doses of nociceptin are found to be pro-anxiety. However, the role of endogenous nociceptin in this process is not fully characterized. Importantly, the role of gender in this process is not known. Thus, the goal of the present study was to assess the role of endogenous nociceptin in anxiety-like behaviors and to determine whether there is a gender-related difference in this response. Mice lacking the prepro-orphanin FQ/prepro-nociceptin gene and their wild-type controls have been generated which represent an ideal model to address these research questions. Thus, using male and female mice of these mice and their wild-type littermates/controls and the elevated plus maze, which is widely used as an animal model of anxiety-like behaviors, we sought to characterize the role of endogenous nociceptin in anxiety-like behaviors. Male and female mice of each genotype were bought to the laboratory and allowed to habituate to the testing room for 1 h. Mice were then tested on the EPM for 5 min, in which each mouse was placed on the elevated plus maze and the amount of time that each mouse remained in the open arms was calculated and compared to their respective wild-type control. Our results showed that older male mice lacking the prepro-nociceptin gene spent significantly lesser amount of time on the open arms compared to their wild-type littermates/controls, showing greater anxiety-like behaviors in these mice. However, this difference was not present between younger male mice of the two genotypes. Furthermore, there was no difference between female mice of the two genotypes at any age. Together, these results suggest

that the endogenous nociceptin system may serve a protective role against the development of anxiety in older mice and there exists a gender related difference in this process.

82. **Neurochemical and behavioral comparison of contingent and non-contingent methamphetamine exposure using binge and long-access yoked self-administration paradigms.** Keck, Thomas M.;[1,2,] Schweppe, Catherine;[1] Burzynski, Caitlin;[1] Ladenheim, Bruce;[1] Cadet, Jean Lud;[1] Gardner, Eliot L.;[1] Xi, Zheng-Xiong Xi;[1] van Praag, Henriette;[3] Newman, Amy H.[1,] [1]NIDA-IRP, NIH, Baltimore, MD USA; [2]Rowan University, Glassboro, NJ USA; [3]NIA-IRP, NIH, Baltimore, MD USA. Abuse of the highly addictive psychostimulant methamphetamine (METH) can cause long-lasting damage to brain monoaminergic systems. Among the profound physical and mental health problems for individual users, METH abuse is associated with cognitive impairments affecting executive function, working memory, and motor performance. Animal models of METH exposure have been useful in dissecting the molecular effects of the drug on cognitive processes, but most studies to date have utilized acute, non-contingent administrations of METH which do not adequately approximate human METH use. Recent reports suggest long-term, contingent METH exposure via long-access (6-hr; LgA) self-administration paradigms may induce cognitive deficits. In this study, we sought to directly compare the differences in behavioral and neurochemical outcomes of rats following non-contingent “binge” METH administration with rats that received chronic METH via contingent or yoked (non-contingent) LgA METH self-administration in order to better understand the role of contingency and patterns of exposure in METH-induced cognitive impairments. Compared to saline controls, METH reduced striatal dopamine and hippocampal 5-HT levels in binge animals but not LgA animals. Hippocampal BDNF levels were reduced in both binge animals and LgA animals; however, hippocampal TrkB levels were increased only in binge animals. No clear deficits were seen in Y-maze or novel object recognition experiments, but contingent LgA animals had decreased performance in a Morris water maze task of spatial learning and memory. These results show that the pattern of drug exposure and the contingency of administration can differentially affect neurochemical outcomes and behavior in cognitive tasks. Research was supported by the National Institute on Drug Abuse-Intramural Research Program, National Institutes of Health.

83. **Viral-mediated overexpression of miR-495 in the nucleus accumbens shell reduces addiction-related gene expression and motivation for cocaine.** Bastle, R.M.[1], Pentkowski, N.S.[1], Chaudhury, T.[1], St. Peter, M.[1] Smith, C.D.[1], Galles, N.[1], Leslie, K.R.[1], Oliver R.J.[2], Gardiner, A.S.[2], Perrone-Bizzozero, N.I.[2], Neisewander, J.L.[1, 1] School of Life Sciences, Arizona State University, Tempe, AZ 85287-1104, USA. [2] Dept. Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM, 87131, USA. MicroRNAs (miRNAs) are considered “master regulators” of gene expression due to their ability to post-transcriptionally suppress several genes simultaneously. Thus, miRNAs may be used as tools to regulate several cellular pathways that are dysregulated in complex neuropsychiatric disorders, such as drug addiction. We previously found through *in silico* analysis that miR-495 targets several addiction-related genes (ARGs), is preferentially expressed in the striatum, and is downregulated by acute cocaine administration selectively in the nucleus accumbens (NAc). We also reported that lentiviral-mediated overexpression (OE) of miR-495 in the NAc shell (NAcsh) of rats reduces ARG expression and intake on a progressive (PR), but not fixed (FR), ratio schedule of cocaine reinforcement. These findings suggest that miR-495 decreases ARG expression in the NAcsh resulting in a decrease in motivation to self-administer cocaine. Here, we sought to verify that our effects were specific for drug motivation by testing whether miR-495 OE reduced motivation for a natural reinforcer. Following FR training to lever press for food pellets, adult male Sprague-Dawley rats were infused with a lentiviral vector containing either GFP (LV-GFP; control) or pri-miR-495+GFP (LV-miR-495) into the NAcsh and were then tested on a PR schedule of food reinforcement. We

found no difference between viral groups in PR responding, suggesting our previous effects on motivation were specific to cocaine. Next, we tested a separate group of rats for the effect of miR-495 OE in the NAcsh on other measures of cocaine-seeking behavior, including a dose-effect function of cocaine self-administration under a PR schedule (0.1875, 0.375, 0.75, 1.5 mg/kg/infusion, IV), extinction of cocaine-seeking behavior, and cue and cocaine-primed reinstatement. Consistent with our previous study, we found an overall reduction in PR responding in the LV-miR-495 group, regardless of cocaine dose. We also found reduced responding in the LV-miR-495 group during the first two days of extinction and during both cue and cocaine-primed reinstatement. The present findings suggest that miR-495 OE specifically attenuates effortful responding for cocaine, but not food, reinforcement. Also, the attenuating effects of miR-495 OE on drug motivation appear to persist in the absence of cocaine. We suggest that miR-495 in the NAc regulates genes involved in motivation both during maintenance of (i.e., “drug-taking”) and abstinence from (i.e., “drug-seeking”) cocaine self-administration. Supported by 1R01DA034097 to NPB and JLN, F31DA035069 to RMB, T32AA014127 to RJO.

84. **Adolescent High Fat Feeding Disrupts Cognitive Flexibility via Downregulation of Reelin in the Prefrontal Cortex (PFC).** Marie A. Labouesse[1], Juliet Richetto[2], Lluís Pujadas[3], Ulrike Weber-Stadlbauer[1,2], Eduardo Soriano[3], Wolfgang Langhans[1], Urs Meyer[1,2. 1]Physiology and Behavior Laboratory, ETH Zurich. [2]University of Zurich. [3]University of Barcelona. High-calorie high-fat diets (HFD) have emerged as one of the most detrimental physiological stressors of Western societies, whereby they pose widespread consequences on metabolic, neural and behavioral functions. In particular, HFD has long been recognized to elicit disturbances in cognitive functions but so far pertinent studies have essentially focused on the hippocampal formation (HPC), whereas the effects on the PFC have largely been ignored. Here we show that chronic HFD throughout adolescence (but not adulthood) results in PFC-related cognitive abnormalities such as discrimination reversal learning and retention of fear extinction in male mice. Based on the recognized role of the cortical GABA system in neuronal synchronization and related cognitive functioning, we next examined the histological integrity of GABA neuronal subtypes. We identified early and persistent reductions in the immunoreactivity for reelin, an extracellular matrix (ECM) protein implicated in the maturation of forebrain structures. Such deficits were specific to the PFC (absent from the HPC), did not extend to other GABAergic neurons (parvalbumin, calbindin or GAD67-positive) and significantly correlated with cognitive performance. These molecular observations were also associated with changes in the expression of reelin downstream signaling partners such as NMDA subunits and some of the reelin receptors (VLDLR, ApoER2, α3β1 integrin). Using a conditional transgenic model specific to the postnatal forebrain (CamKIIα promoter), we next showed that reelin overexpression effectively prevented the emergence of prefrontal-related cognitive deficits induced by HFD. Importantly, these effects were specific for the PFC because functions associated with striatal and HPC regions were not reverted. Our findings demonstrate that the ECM protein reelin is functionally implicated in the development of PFC cognitive abnormalities after adolescent HFD, and thus provide one of the first putative mechanisms linking nutritional stress to PFC dysfunction. Funding: ETH Zurich, Swiss National Science Foundation.

85. **Exploring the Role of Parasitic Tyrosine Hydroxylase in *Toxoplasma* Behavior Alteration.** Ross McFarland1, Zi Teng Weng2, David Sibley2, Robert Yolken3,4, Mikhail Pletnikov3. 1Johns Hopkins Bloomberg School of Public Health, 2Washington University in St. Louis, 3Johns Hopkins University School of Medicine, 4Stanley Medical Research Institute. Infection with the neurotropic parasite *Toxoplasma gondii* has been known to be a risk factor for the development of schizophrenia in humans, and to impact rodent performance on several behavioral assays. Recent evidence in the

Toxoplasma genome, supported by imaging and expression data, has shown that the parasite produces the dopamine generating enzyme tyrosine hydroxylase, and that in the immediate presence of the parasite in mouse brain tissue, levels of dopamine are increased. These data suggest an important role for this genetic element in changing host brain chemistry and impacting behavior. Our lab was given access to parasite strains with a knockout of the tyrosine hydroxylase gene, and used these strains to determine if the production of this enzyme was necessary to induce the behavioral phenotype associated with Toxoplasma infection. The results showed a promising trend, suggesting that disruption of the tyrosine hydroxylase region may cause a shift in the presentation of behavioral change associated with infection. Furthermore, our work highlighted a previously unobserved phenomenon whereby infection with a genetically intact Toxoplasma pathogen caused a functional loss of drug effect following the administration of amphetamine. Animals suffering from chronic infection with genetically undisturbed Toxoplasma showed no significant increase in activity after being administered high levels of the stimulant amphetamine, suggesting a very interesting potential interaction between the parasite and brain function.

86. **Sodium butyrate increases contextual fear expression in sign- but not goal-trackers.** Christopher J. Fitzpatrick[1], Marcelo A. Wood[2], and Jonathan D. Morrow[1,3]**.** [1] Neuroscience Graduate Program, University of Michigan, Ann Arbor, MI 48109, USA; [2] Department of Neurobiology and Behavior, University of California at Irvine, Irvine, CA 92697, USA; [3] Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109, USA. Pavlovian conditioned approach behavior has been previously used to identify rats that display enhanced fear expression in response to either cues (sign-trackers; STs) or context (goal-trackers; GTs) following fear conditioning (FC). Levels of histone acetylation in brain regions such as the dorsal hippocampus (dHPC) are critical in consolidating contextual FC and may underlie individual variation in contextual fear expression. Therefore, we hypothesized that low levels of contextual fear expression in STs are a result of decreased acetylation following contextual FC. In Experiment 1, we showed that STs express less contextual fear than GTs following contextual FC, despite equal levels of contextual fear during conditioning. In Experiment 2, we demonstrated that sodium butyrate (200 mg/kg; 10 mL/kg), a histone deacetylase (HDAC) inhibitor, given 1 h prior to contextual FC, enhances contextual fear expression in STs, but not GTs. This is the first demonstration that a HDAC inhibitor given before contextual FC can enhance contextual fear expression in some subjects but not others, and suggests that individual variation in histone acetylation during contextual fear conditioning may underlie individual variation in contextual fear expression. In addition, these results may contribute to a neurobiological explanation of why some individuals but not others develop posttraumatic stress disorder. *This work was funded by the University of Michigan* Department of Psychiatry (U032826; J.D.M.), the National Institute on Drug Abuse (R01 DA036984; M.A.W.), and the Department of Defense National Defense Science and Engineering Graduate Fellowship (C.J.F.).

Saturday, June 6

8:00-10:00 **Sensory processing in autism – from the clinic to animal models.** Chair: **Susanne Schmid.**

Basic information processing deficits in autistic children. Bob Oranje, PhD (1,2), Gitte Falcher Madsen, MD, PhD (3), Chantal Vlaskamp, MSc (1), Jens Richardt Jepsen, PhD (2;4), Sarah Durston, PhD (1), Cathriona Cantio, MSc (3), Birte Glenthøj, MD, DM.Sc. (2), and Niels Bilenberg, MD, PhD (3). Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands. Center for

Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Copenhagen University Hospital, Psychiatric Center Glostrup, Denmark; Faculty of Health Sciences, University of Copenhagen. Department of Child and Adolescent Mental Health Odense, Research Unit (University function), Mental Health Services in Region of Southern Denmark, Faculty of Health Sciences, University of Southern Denmark. Center for Child and Adolescent Mental Health Capital Region, Copenhagen, Denmark. Objective: Autism spectrum disorders (ASD) and schizophrenia are separate disorders, but there is evidence of conversion or comorbid overlap. The objective of this study was to explore whether deficits in sensory gating and mismatch negativity (MMN) as seen in some patients with schizophrenia, can also be found in a group of ASD children compared to neuro-typically developing (NTD) children. Methods: In a case-control design, 35 ASD (infantile autism, N=11; Asperger's syndrome, N=7; PDD NOS, N= 17) children and 40 healthy NTD controls (8-12 years) were assessed in the same physiological test battery, the CPTB (Copenhagen psychophysiological test battery). Besides a MMN paradigm, the CPTB also consists of paradigms to assess prepulse inhibition of the startle reflex (PPI), P50 suppression, and selective attention. We screened for differences between groups as well as between the three different subcategories within the ASD group. Data on selective attention has not yet been analysed. Results: We found reduced mismatch negativity and P50 amplitude in our group of ASD children compared to the typically developing children. In addition, we observed increased sensorimotor gating and sensitization in the ASD subjects. Most of these deficits appeared to be based on one subcategory of ASD patients only, although the specific subcategory differed per affected paradigm. Conclusion: Similarly to what is usually reported for patients with schizophrenia, we found reduced mismatch negativity and P50 amplitude in the ASD children compared to the typically developing children. However, in contrast to what is usually found in schizophrenia, we found normal sensory gating, while both sensorimotor gating and sensitization were increased in the ASD subjects. Our data support the idea of partial overlap between ASD and schizophrenia. Future research should point out whether the observed abnormalities in sensorimotor gating and sensitization are specific (endophenotypic) for ASD. Acknowledgement: None of the authors have a conflict of interest.

Auditory hypersensitivity in Fragile X Syndrome. Khaleel Razak, Teresa Wen, Jonathan Lovelace, Sarah Reinhard, Mike Hsu, Devin Binder, Iryna Ethell. University of California, Riverside. Fragile X Syndrome (FXS) is the most prevalent cause of inherited intellectual disability and is a leading genetic cause of autism. Data from humans with FXS and the mouse model of FXS (*Fmr1* KO, henceforth 'KO') consistently indicate significant auditory processing deficits including the common phenotype of auditory cortical hyper-excitability. Sensory hypersensitivity is also common in autism and is one of the diagnostic criteria in DSM V. The mechanisms of auditory hypersensitivity at the circuit and molecular levels are unknown. I will discuss studies that show abnormalities in auditory cortical *in vivo* single unit responses as well as sound evoked EEGs from the Fmr1 KO mice. Specifically, cortical neural responses to tones in KO mice are significantly longer lasting compared to WT neurons, indicating an inability of KO cortex to shut down their responses following a phasic onset-related burst. This is may be a correlate of behavioral hypersensitivity. In addition, KO cortex neurons show broader frequency tuning curves that may be a correlate of observations in human auditory cortex that a larger region of cortex is activated for a given sound in FXS patients compared to control patients. Sound evoked EEG responses in KO mice show an increase in the amplitude of NI component and a dramatic reduction in the ability of responses to habituate to repetitions of the same sound. These two phenotypes are identical to those observed in humans with FXS indicting the potential of EEG responses as a translation-relevant biomarker. We have begun to address the molecular/synaptic mechanisms that may underlie auditory cortical deficits in the KO mice and observe differences in dendritic spine maturation, inhibitory neuron and associated extracellular matrix development and levels of matrix metalloproteases during auditory critical periods. The relevance of these data to auditory hypersensitivity development and potential for drug development based on these findings will be discussed. Funded by the National Institutes of Health (grant 1U54HD082008-01).

Sensory filtering and cognitive function in a rat model for autism. Theshani deSilva, Susanne Schmid. Anatomy & Cell Biology, University of Western Ontario, Canada. Children with autism spectrum disorders are reported to show alterations in sensory processing. Many are hyper-sensitive to acoustic stimulation, and show disruptions in habituation to repeated sound. We have been studying sensory filtering mechanisms, namely habituation, for many years and have reported an important role for cholinergic neurotransmission as well as a calcium- and voltage-activated big conductance potassium channel (BK channel) in habituation. We here use a Long Evans rat model for autism, a single prenatal injection of valproic acid (VPA) at gestation day 12.5, in order to study sensory filtering disruptions associated with autism and the impact of these disruptions on attention. Adolescent VPA rats show reduced exploratory behavior and severe disruption of habituation in both exploratory behavior and acoustic startle responses. In accordance to observations in autistic patients, these disruptions subside in adult animals. Also in accordance with most human studies, VPA animals show only very mild –if any- deficits in prepulse inhibition, restricted to low prepulses and short intervals. VPA animals are significantly slower in learning a 5-choice serial reaction time task (5-SRTT) measured in Bussey touch-screen boxes, and even if maximally trained they reach only a lower level of accuracy (58±3.5% in VPA versus 72±3.5% in control animals). This is mainly due to an increased level of premature responses (75%±18% of errors in VPA versus 33±4% in control) and lower levels of omissions (10.8%±2.7 versus 23.4±4.9%), indicating an increased impulsivity in VPA animals. Interestingly, an auditory distraction during the attention period significantly reduced the performance in control rats from 72±3.5% to 60±3.5% accuracy, but not in VPA animals (from 58±3.5% to 56±3.5% accuracy). Injections with the acetyl choline esterase inhibitor galantamine before testing did not alter any of the 5-CSRTT measures. Future studies will test other drugs, most importantly a positive BK channel modulator and the often prescribed drug methylphenidate (Ritalin) on sensory filtering and attention.

Preclinical assessment of In vivo electrophysiological phenotypes related to autism spectrum disorders. Steven Siegel[1], Michael Gandal[1], Eddie Billingslea[1] [1]University of Pennsylvania, Philadelphia, PA, U.S.A. Introduction: Recent studies suggest that abnormalities in glutamate and GABA signaling contribute to the constellation of deficits in autism spectrum disorders and related conditions. These deficits can be measured using electroencephalographic (EEG) including both event related potentials (ERPs) and power within specific frequency ranges. Furthermore, clinical studies suggest that a subset of these EEG biomarkers is associated with symptoms. This presentation will address the relationship between gamma-band activity and social/cognitive behaviors in preclinical models of GABergic and NMDA-receptor-mediated glutamate hypofunction as well as how these models can be used to screen therapies. Methods: Data from patients with autism will be juxtaposed with data from animal model mice. Subsequently, EEG and behavioral data from of mice with disruption of the NMDA receptors in excitatory and/or inhibitory neurons, as well as those treated with prenatal Valproic Acid will be compared to the pattern of deficits in autism. Data following exposure to potential therapeutic agents including GABA B agonists and mGluR antagonists will also be presented. Results: Elevated resting gamma power was associated with deficits in social interactions. Consistent with an elevated baseline noise, excitatory neurons from transgenic mice showed increased intrinsic excitability in patch studies. A $GABA_B$-receptor agonist reduced excitability, improved gamma-band responses, and reversed behavioral deficits in model mice. Conclusions: Data suggest that baseline gamma power is associated with disruption of social function and that $GABA_B$ agonists may be useful for autism.

8:00-10:00 **The mechanisms of stress resilience and safety: Implications for stress-related neuropsychiatric disease.** Chair: **Matthew W. Hale.**

Prefrontal control of resilience to adverse events. Michael V Baratta[1]. [1]Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, Colorado, USA. The outcome of an adverse event can vary widely between individuals, and many of the factors determining vulnerability and resilience to the impact of an adverse event revolve around coping factors. Perceived ability to exert

behavioral control over the adverse event is central to coping, and the neural mechanisms that mediate this process are the focus of this presentation, as studied in an animal model. Behavioral control over stress not only blunts the impact of the adverse event being controlled, but also alters the organism's response to future negative circumstances. These stress-buffering effects of behavioral control are enduring, trans-situational, and activate a distinct neural circuit that includes the ventral medial prefrontal cortex (mPFCv). Research suggests that the *detection* of behavioral control and the *subsequent use* of control information to regulate stress-responsive structures are mediated by separate mPFCv cell populations. Additionally, engagement of the mPFCv by behavioral control is able to impact later inhibitory learning as evidenced by accelerated extinction of conditioned responses to both fear- and drug-associated environments. Collectively, this line of research may serve to identify circuit-level changes underlying the formation of resilience and provide a mechanistic explanation for positive treatment outcomes observed in psychiatric conditions such as anxiety and substance-use disorders. Support: R01 MH050479; T32 DA017637; NARSAD Young Investigator Grant 21663.

Insular contributions to stress and fear reduction by safety signals. John P. Christianson[1, 1]Boston College, 140 Commonwealth Avenue, Chestnut Hill, MA USA. The consequences of traumatic and stressful events entail both unconditioned and conditioned mechanisms. Discrete cues that allow an animal to predict when danger is unlikely, "safety signals", modulate the unconditioned effects of stress on anxiety-like behavior and can alter the later expression of conditioned fear. In a variety of paradigms and approaches we demonstrate that the posterior insular cortex is critical to these effects of safety signals. Specifically, lesions, pharmacological inhibition, and NMDA receptor blockade within the insular cortex abolish the protective effects of safety signals on stressor induced anxiety and conditioned inhibition of fear. I will present a hypothetical "safety learning circuit" in which the insular cortex contributes an error signal when danger is expected, but does not occur. This model aligns with a large body of human research into insular cortex functions in detecting salience. Funding for the research was provided by the National Institute of Mental Health grants MH093412, MH082453A and the Brain and Behavior Research Foundation.

Amygdalocortical circuitry contributes to discriminative reward, fear and safety learning. Sangha, Susan[1, 1]Department of Psychological Sciences, Purdue University, West Lafayette, IN, USA. Accurate discrimination of environmental cues predicting reward, fear or safety is important for survival. The amygdala, prelimbic and infralimbic cortices are implicated in regulating reward-seeking and fear behavior; however, no studies have examined their roles in discriminating among reward, fear and safety cues. Using a discriminative conditioning task that includes presentations of a reward cue (paired with sucrose), fear cue (paired with footshock) and a compound fear+safety cue (no footshock) within the same sessions allowed us to assess the flexibility and precision of fear and reward-seeking behaviors to these cues. Single unit recordings made in the rat basal amygdala showed neurons discriminate among reward, fear and safety cues. One particular population of neurons showed a selective response to only the safety cue, demonstrating safety selective neurons in the basal amygdala. Local, reversible inactivations of the prelimbic or infralimbic cortex yielded differential results: inactivating the prelimbic cortex blunted discriminatory reward seeking whereas infralimbic cortical inactivation impaired discrimination between the fear and safety cues. Together these results imply that the amygdalocortical circuitry contributes to precise discriminative reward, fear and safety learning.

An immunization strategy for prevention of stress-related neuropsychiatric disease. Christopher A. Lowry, University of Colorado Boulder. Novel prevention and treatment strategies are urgently needed to reduce the burden of stress-related psychiatric disorders, including post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). Both preclinical and clinical studies suggest that inflammation

increases vulnerability to development of anxiety and affective disorders. Consequently, immunoregulatory strategies to decrease inflammation have potential for the prevention and treatment of these disorders. Using a murine model of chronic psychosocial stress, the chronic subordinate colony housing (CSC) model, we found immunization with a heat-killed preparation of *Mycobacterium vaccae*, a bioimmunomodulatory agent previously shown to activate regulatory T cells (Treg) and to increase production of anti-inflammatory cytokines, prevented development of a PTSD-like syndrome. Immunization with *M. vaccae* antigen induced a more proactive emotional coping style during exposure to a dominant aggressor, and, in association with suppression of proinflammatory cytokine secretion, prevented stress-induced development of spontaneous colitis and aggravation of colitis in a model of inflammatory bowel disease. Furthermore, immunization with *M. vaccae* antigen prevented development of a fear-like state and enhanced fear extinction. Preliminary analysis suggests that the protective effects of *M. vaccae* immunization are due to protection from a stress-induced proinflammatory gut microbial community. Consistent with this hypothesis, protective effects of immunization were absent following Treg depletion. These data provide a hypothetical framework for development of novel strategies for prevention of stress-related psychiatric disorders in vulnerable individuals.

10:30 **Presidential Lecture. Stephen Kent**, La Trobe University, Melbourne, Australia. Should we all eat less? Behavioural, endocrine, and immunological consequences of calorie restriction

Should we all eat less? Behavioural, endocrine, and immunological consequences of calorie restriction. Kent S. School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia. Calorie restriction (CR) has been shown to increase longevity and elicit many health promoting benefits including delaying immunosenescence and attenuating neurodegeneration in animal models of Alzheimer's disease and Parkinson's disease. However, the mechanisms underlying these effects are unknown, but a decreased inflammatory state may be a contributor. Data presented in this talk will highlight how reduced food intake (50% for 28 days), which still meeting the RDAs for all vitamins and minerals, reduces anxiety-like behaviour, increases social behaviour, alters sexual selection, changes endocrine levels, and shifts hypothalamic signaling pathways to an anti-inflammatory bias. This results in an attenuated fever and sickness response to lipopolysaccharide (LPS), the active fragment of Gram negative bacterial cell walls. Associated with this attenuated immune response are increases in anti-inflammatory compounds (e.g., corticosterone, NPY, interleukin-10) and decreases in pro-inflammatory compounds (e.g., cyclooxygenase-2, interleukin-6, leptin). Our most recent work has focused on the ability of CR to attenuate microglial activation primarily in the arcuate nucleus and ventromedial nucleus of the hypothalamus. Collectively, our results indicate that microglial activation may be dependent on NPY-associated changes in brain and/or body temperature, suggesting that the thermoregulatory effects of NPY may represent a key mechanism underlying the CR-induced suppression of neuroinflammation. Achieving a greater understanding of the mechanisms involved in the CR induced suppression of fever and neuroinflammation may contribute to the development of therapeutic strategies that mimic the anti-inflammatory effects of CR, thus providing potential benefit for the treatment and management of chronic inflammatory conditions, autoimmune disease, and neuroinflammatory diseases.

1:00-3:00 **Modulation of memories and flexibility in reward-related learning: From circuits to boutons in the rodent prefrontal cortex.** Chair: **Susan L. Andersen.**

Role of the rat medial prefrontal cortex in decisions involving effort, reward, and contingency. David R. Euston, University of Lethbridge, Canada. The mPFC has been implicated in many cognitive roles including effort-reward decision making, goal-directed actions, and attentional set shifting. My lab has been examining the role of mPFC in each of these domains. Within the realm of effort-reward decisions, it has been shown that rats with lesions of the dorsal mPFC (specifically, anterior cingulate cortex; ACC) are less willing to work for reward. However, this finding relies almost exclusively on a

climbing-based task. When tested with other forms of effort (i.e., weight lifting or crossing an exposed open field) rats show little impairment. Further, careful examination our ramp-climbing results suggests that the deficit in lesioned animals is not in the initial decision but rather in persistence towards a goal when faced with an impediment. For the mid-ventral mPFC (prelimbic cortex; PL), two roles have been proposed: goal-directed action and attentional set-shifting. To examine the role of PL in value-based decisions, we have tested animals in a variant of the "N-arm bandit" task, in which rats choose between three locations which offer differing amounts of reward. The reward values change randomly every 35 trials and rats have to learn the new values through trial and error. Many rats with mPFC lesions were strongly biased to specific reward arms and were thus less likely to switch based on reward. Our results are thus completely consistent with a role of mPFC in goal-directed action. In the realm of attentional set-shifting, we hypothesized that the observed deficits in such tasks are due to a fundamental difficulty in detecting the partial degradation of contingency between cues and reward which is an integral aspect of set-shifting experiments. Preliminary results suggest that contingency degradation also impairs reversal learning, undermining the idea that the primary role of PL is to shift attention from one perceptual dimension to another. In sum, we find evidence that mPFC is important for persistence towards a chosen goal and in adjusting that goal once it no longer consistently leads to an optimal outcome. Supported by Alberta Innovates: Health Solutions and Natural Sciences and Engineering Research Council of Canada.

Prefrontal GABA regulation of cognitive and emotional functions and its relevance to schizophrenia. Stan B. Floresco. University of British Columbia. Alterations in GABA markers in the prefrontal cortex (PFC) are arguably one of the most reliable forms of neuropathology associated with schizophrenia. Numerous animal models of the disorder also disrupt PFC GABA activity, causing a "noisy" cortex. Yet an understanding of how PFC GABA activity may regulate cognitive and emotional functions that are perturbed in schizophrenia remains limited. To address this issue, we assessed the effects of pharmacological reduction of PFC $GABA_A$ transmission in rats, using a battery of translational assays of cognitive, emotional and executive function that are relevant to schizophrenia. Reducing PFC GABA activity impaired set shifting, yielding perseverative and non-perseverative impairments, similar to what has been observed in schizophrenic patients. These treatments also impaired spatial reference and working memory, even though inactivation of the PFC did not affect these functions. The qualitative nature of these deficits bear a striking resemblance to those reported by studies using back-translational approaches with patients. Affective functioning was assessed with different aversive conditioning assays. PFC disinhibition markedly disrupted discriminative fear learning, resulting in increased fear to a neutral stimulus and reduced fear to an aversive one, indicative of an impairment in affective salience attribution. Again, these effects were nearly identical to those observed in schizophrenia. Moreover, amphetamine-induced locomotion and increased phasic firing of midbrain dopamine neurons were enhanced by these manipulations, suggesting that disinhibition of the PFC may also contribute to hyperdopaminergia associated with the disorder. Collectively these data indicate that reducing PFC GABA transmission induces a variety of cognitive, executive and affective abnormalities that are qualitatively similar to disturbances observed in schizophrenic patients. Moreover, these effects are distinct from those induced by suppression of PFC activity, indicating that a "noisy" cortex may in some instances interfere with cognitive/affective functions not normally regulated by the frontal lobes. These results provide novel insight into how PFC GABA hypofunction may underlie many of behavioral and neurochemical abnormalities observed in schizophrenia, and suggests that this pathophysiology may contribute to both positive and negative symptoms. Supported by a grant from the Canadian Institutes of Health Research.

The role of dopamine D1 and noradrenergic Alpha2A receptors on the development of working memory. Susan L. Andersen[1,2] [1] McLean Hospital and [2] Harvard Medical School, Belmont, MA, USA. Working memory is an integral function of cognition. Similar to humans, working memory in rats improves

with maturation between the juvenile, postnatal day (P)21, to young adulthood of P90. The novel object recognition task has been used to assess development of working memory in preclinical studies. In this task, subjects are familiarized to two objects and then one object is replaced with a novel object in a later trial. The time spent investigating each object is an indicator of working memory and is mediated primarily by dopamine and noradrenergic systems in the prefrontal cortex (PFC) and the hippocampus. The latter region encodes the spatial location of the object. Increased activity at the D1 receptor in the PFC disrupts working memory, whereas Alpha-2A (A2A) receptor activity improves function in adult animals. Less is known in immature systems, although we recently found that A2A activity reduces impulsive choice. To better understand how PFC D1 and A2A receptors influence novel object recognition, lentiviral vectors that specifically overexpressed these receptors or green fluorescent protein (GFP) in glutamatergic neurons by the CamKinase IIa promotor (CK) were used. Separate groups of male and female juvenile rats received stereotaxic injections of CK.D1, CK.A2A, or CK.GFP virus into the prelimbic region of the PFC (location verified with histology). Novel object recognition was tested 5 days later at P26 to allow for sufficient receptor expression. Using a corner-less, oblong testing chamber, subjects were habituated to the arena for a discrete 6 min trial; trials 2 and 3 included the familiar objects within the arena; on the fourth trial, one novel object replaced a familiar object. Each trial was separated by a 3 min inter-trial interval. Time spent exploring each object was recorded. Subjects were placed back into the area 24 h later, but this time one familiar object was moved to test spatial memory. CK.D1 disrupted novel object recognition relative to CK.GFP animals, but had minimal effects on spatial localization. Females were more affected than males, consistent with our previous observations that females are more sensitive to D1 manipulations. In contrast, CK.A2A males and females demonstrated significant improvement in novel object recognition compared with CK.GFP subjects. Our findings localize previous effectiveness of the A2A antagonist yohimbine to improve working memory in young rats to the prelimbic PFC. As increased impulsivity and impaired cognition are predictive of elevated risk for substance use, treatment with an A2A agonist early may reduce or prevent drug use if given during a sensitive period of development. Acknowledgements: Supported by R01s DA-015403 and DA-026485 to SLA.

Structural plasticity of orbital frontal cortex axons during rule learning. Linda Wilbrecht[1,2], Carolyn Johnson[3], Hannah Peckler[1], Lung-Hao Tai[1. 1]UC Berkeley Department of Psychology, [2]Helen Wills Neuroscience Institute, and [3]UC San Francisco Neuroscience Graduate Program. Rules are learned associations organized to guide conduct or action in search of a goal. In dynamic situations, a balance between exploitation of established rules and exploration of alternate options is essential for adaptive behavior. Rules are thought to be updated based on differences between expected and actual outcomes. These differences, formally called prediction errors, can be used to scale adjustments in behavior presumably by remodeling associations between cues, actions and outcomes. It is often assumed that rule learning and rule updating are reflected anatomically at the level of individual synapses in association cortex, but in vivo evidence for this is lacking. The orbitofrontal cortex (OFC) and dorsomedial prefrontal cortex (dmPFC) likely encode cue-outcome and action-outcome expectancies respectively and have been identified as hubs critical for flexible updating of behavior. We hypothesized that rule learning would modify long range axonal projections from the OFC to the dmPFC and furthermore that structural plasticity would scale with prediction errors estimated from choice history. To this end, we trained mice to learn rules in a multiple choice foraging and reversal task (Johnson and Wilbrecht, 2011) and daily imaged OFC axons that project to the dmPFC. Here we show that rule training significantly enhanced structural plasticity of boutons on axons projecting from OFC to dmPFC, while other forms of enrichment did not. The density of boutons before training and experience-dependent new bouton gain were both correlated with learning and exploitation of a rule. Throughout training, greater prediction errors and

exploratory behavior correlated with bouton loss. Our data reveal a structural trace of rule learning and illuminate neural correlates of individual differences in decision making history and strategy.

1:00-3:00 **Neuromodulatory control of arousal and motivation by ascending peptidergic systems.** Chair: **Andrew L. Gundlach.**

Neuromodulatory control of arousal and motivation by ascending peptidergic systems. Andrew L. Gundlach[1-3. 1]Neuropeptides and Behavioural Neuroscience Divisions, The Florey Institute of Neuroscience and Mental Health, [2]Florey Department of Neuroscience and Mental Health, [3]Department of Anatomy and Neuroscience, The University of Melbourne, Victoria, Australia. A primary function of the brain is to generate optimal behavioural responses to diverse sensory and environmental cues. In this context, an array of neuromodulators, including monoamines, peptides and growth factors, regulate a range of behavioural and physiological traits, including emotion, sleep, motivation, and learning and memory. Neuromodulation, while essential to CNS function, has been more difficult to study than classical transmission, but in recent years, dramatic progress has been made in mapping neuromodulatory circuits, physiological analysis of circuit dynamics, and interrogation of circuit function using genetic, viral, and imaging methods. These interdisciplinary studies have improved knowledge of how fundamental neural circuits are modulated to generate adaptive behaviours. Relaxin-3 is a neuropeptide member of the insulin/relaxin superfamily and its cognate G-protein-coupled receptor is RXFP3. Research over the last decade has elucidated the distribution and putative biological functions of relaxin-3/RXFP3 signalling networks, including interactions with modulatory systems such as oxytocin/vasopressin, CRF, orexin and serotonin. The relaxin-3/ RXFP3 system is not widely investigated, so this symposium will highlight its broad putative roles in the regulation of general arousal, feeding and body weight homeostasis, stress-related depressive- and anxiety- behaviour, and in drug seeking (see refs). Specifically, I will introduce the neural targets of relaxin-3/RXFP3 and the anatomical basis for its arousal network status; *Elena Timofeeva* (Canada) will discuss diet- and sex-specific aspects of relaxin-3 neuron activity and RXFP3 plasticity in food intake regulation in rats; *Craig Smith* (Australia) will review data suggesting relaxin-3/RXFP3 signalling promotes motivational drive and stress resilience in mice; and *Anna Blasiak* (Poland) will elaborate neural mechanisms that underlie behavioural effects of RXFP3 activation on feeding and stress responses, with a focus on *in vitro* electrophysiological studies of hypothalamic PVN neurons in rats. These preclinical data indicate RXFP3 might be a novel target for treatment of the dysfunctional neural homeostasis that occurs in anxiety, addiction and depression. Lenglos C, Mitra A *et al*. (2013) Genes Brain Behav 12, 370-87. Ma S, Blasiak A *et al*. (2013) J Physiol (Lond) 591, 3981-4001. Ryan PJ*, Kastman HE* *et al*. (2013) PNAS (USA) 110, 20789-94. Smith CM, Chua BE *et al*. (2014) Behav Brain Res 268, 117-26.

The role of relaxin-3 in food intake regulation: diet and sex-specific aspects. Timofeeva, Elena; Calvez, Juliane; Lenglos, Christophe; De Avila Dal'Bo, Camila. Faculté de Médecine, Département de Psychiatrie et de Neurosciences, Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec, Université Laval, Québec (QC), G1V 0A6, Canada. Relaxin-3 is a neuropeptide strongly expressed in the nucleus incertus (NI). The NI neurons largely innervate forebrain structures where relaxin-3 binds with high affinity to its cognate receptor RXFP3. The present studies investigated expression of relaxin-3 and its specific receptor RXFP3 in hyperphagic rat models. The first hyperphagic model was diet-induced obesity (DIO) induced in about tertile of Sprague Dawley (SD) rats fed high-energy diet. The DIO rats showed higher expression of relaxin-3 in the NI, however lower expression of RXFP3 in the majority of the forebrain regions. Therefore, the effects of strong expression of relaxin-3 may be balanced by lower expression of RXFP3 in DIO rats in normal feeding conditions. The DOI rats strongly defend their elevated body weight against caloric restriction by a significant increase in food

intake after food deprivation. Interestingly, during refeeding after food deprivation the DIO rats along with increased expression of relaxin-3 in the NI significantly increased the levels of expression of RXFP3 in food intake regulating brain regions. The second model used in these studies was hyperphagia induced by repeated episodes of food restriction and stress. These conditions induced strong hyperphagia in female but not male SD rats. Hyperphagic female rats showed high expression of relaxin-3 in the NI. Sex-specific effects of relaxin-3 were further addressed by direct intracerebroventricular (icv) injections of relaxin-3 in male and female SD rats. Relaxin-3 induced an increase in food intake in male and female rats; however the orexigenic effects of relaxin-3 were significantly stronger in female compared to male rats. In male, but not female rats relaxin-3 strongly activated the hypothalamic-pituitary adrenal (HPA) axis. Conversely, female rats showed stronger expression of corticotropin-releasing factor in the bed nucleus of the stria terminalis in response to icv injections of relaxin-3. In summary, these studies showed increased activity of the relaxin-3 system in hyperphagic rat models. In male rats, relaxin-3 increased food intake and strongly stimulated the HPA axis activity. In female rats, the orexigenic effects of relaxin-3 were significantly stronger while the effects on HPA axis activity were significantly lower compared to male rats. The results suggest the important role of relaxin-3 in food intake regulation in obesity and stress-induced eating disorders.

Relaxin-3/RXFP3 signalling promotes motivational drive and stress resilience in mice. Craig M Smith[1,2,4], Ihaia T Hosken[1,4], Andrew W Walker[1,2,4], Berenice E Chua[1], Cary Zhang[1,4], Derek A Denton[3], Michael J McKinley[3], Andrew J Lawrence[2,4], Elena Timofeeva[6], Andrew L Gundlach[1,2,4,5.] [1]Neuropeptides, [2]Behavioural Neuroscience and [3]Neurophysiology Divisions, The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia, [4]Florey Department of Neuroscience and Mental Health and [5]Department of Anatomy and Neuroscience, The University of Melbourne, Melbourne, Australia, [6]Department of Psychiatry and Neuroscience, Laval University, Quebec, Canada. The neuropeptide relaxin-3 is expressed by broadly projecting neurons within the pontine *nucleus incertus*, and signals through its widely expressed G-protein coupled receptor, RXFP3. Anatomical and functional evidence indicates that relaxin-3/RXFP3 signalling can modulate a range of limbic, septohippocampal, and hypothalamic circuits to influence motivation, stress responses, and other modalities related to behavioural arousal. Our studies have used transgenic and wild-type (WT) mice, in combination with newly developed pharmacological and viral tools, to further investigate the role of relaxin-3/RXFP3 signalling in behavioural control. Firstly, motivational drive was assessed. Central injections of RXFP3 antagonist reduced motivated food seeking ($p<0.05$) and consumption ($p<0.001$) in WT mice, while in salt (sodium) depleted WT mice, RXFP3 antagonist treatment reduced the motivation to consume a 0.3 M NaCl solution ($P<0.001$) – an effect also observed in sheep ($P<0.001$). Furthermore, relaxin-3 and RXFP3 knockout (KO) mice displayed reduced motivation to run on voluntary home-cage running wheels ($p<0.001$), and to press a lever to obtain sucrose reward in an operant chamber ($p<0.05$). Secondly, stress resilience was assessed, revealing that relaxin-3 and RXFP3 KO mice were hypersensitive to stress-induced insomnia ($p<0.001$) and stress-induced changes in alcohol consumption ($p<0.05$), respectively. Furthermore, central infusion of an RXFP3 agonist reduced elevated levels of anxiety-like behaviour induced in WT mice by the benzodiazepine receptor inverse agonist, FG-7142. To better determine the potential mechanisms which underlie these actions, the neurochemical phenotype of RXFP3 neurons was assessed using mice which express yellow fluorescent protein within RXFP3-positive neurons (RXFP3-eYFP). These studies have revealed some important insights. For example, relaxin-3/RXFP3 signalling may influence hippocampal activity via modulation of calretinin positive neurons within the hilar region of the ventral dentate gyrus. Taken together, these studies provide further evidence that relaxin-3/RXFP3 signalling influences key neuronal circuits to promote motivational drive and stress resilience. As these modalities are often disrupted in affective disorders such as depression, these studies highlight the potential of relaxin-3/RXFP3 systems as a therapeutic target.

Relaxin-3/RXFP3 networks in food intake and stress responses – neural mechanisms underlying behavioural effects. Anna Blasiak[1], Alan Kania[1], Marian H. Lewandowski[1], Andrew L. Gundlach[2]
[1]Department of Neurophysiology and Chronobiology, Jagiellonian University, Krakow, Poland, [2]The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Australia
An overabundance of stressors in everyday life and free access to highly-rewarding, high-caloric foods are considered significant causes of obesity in modern societies. Indeed, obesity is a leading preventable cause of death globally; so a better knowledge of neural mechanisms responsible for disturbances in energy homeostasis that lead to eating disorders is important. However, the identity of all the neurochemicals and neural substrates underlying stress and reward-related behaviours is not known and effective treatments of obesity are still required. Soon after its discovery, the first identified physiological effect of icv injections of the neuropeptide, relaxin-3, was an increase in food intake in satiated adult rats, with a similar potency to canonical orexinergic peptides such as NPY. Furthermore, relaxin-3-expressing neurons located in the *nucleus incertus* (NI) within the posterior ventromedial central grey, are responsive to a range of stressors, making the relaxin-3 system a good candidate for linking stress and stress-related feeding. However, the nature of interactions between NI/relaxin-3 neurons and other neural circuits controlling energy homeostasis and stress responses remain largely unknown. Among brain areas innervated by NI neurons, the hypothalamic paraventricular nucleus (PVN) was implicated in relaxin-3-mediated food intake; and the effects on feeding of acute and chronic intra-PVN administration of native relaxin-3 or potent relaxin-3 receptor (RXFP3) agonist peptides, is thought to be mediated by inhibition of hypothalamic oxytocin (OT) and vasopressin PVN neurons (Ganella DE et al., Behav Pharmacol 23 (2012) 516-25). Recent *in vitro* brain slice experiments demonstrate an potent inhibitory action of RXFP3 agonists (RXFP3-A2, 600 nM) on PVN neurons (42 of 67 neurons tested). Importantly, these effects are direct since they persist in the presence of TTX (1 µM) and glutamate and GABA receptor blockers (10 µM). Notably, several inhibited cells were identified as magnocellular oxytocin-positive neurons and RXFP3 agonist-induced inhibition of parvocellular neurons was also observed. Our data support the hypothesis that relaxin-3/RXFP3 signalling is associated with stress and feeding-related abnormalities, including obesity and binge eating and we are currently exploring further behavioural effects of hypothalamic RXFP3 activation under different dietary and stress conditions. Funding: National Science Centre Poland DEC-2012/05D/NZ4/02984 and Ministry of Science and Higher Education, Poland 0020/DIA/2014/43.

3:30-6:00 **Behavioral Neuroscience through the eyes of those Bob Blanchard influenced.**
Chairs: **Brandon L. Pearson; Cliff Summers.**

The Blanchard Rules: Bob, from A to Z. Caroline Blanchard, The Pacific Biosciences Center, University of Hawaii. Shortly after Bob died, I learned that two recent Ph.D.s from our lab had compiled a list of “Bobisms” over their several years in the lab. These–characteristic utterances or actions or attitudes—added up to form one view of a person who will be vivid in a lot of peoples’ memories for a long time to come. I have, of course, memories of my own. This talk will tap both sources, and some other views as well: Bob provoked reactions. Its goal is to provide a snapshot of a man in whom life and work were unusually well integrated; whose personality encouraged departures from accepted dogma, and for whom curiosity and faith in the power of behavior to integrate and explain evolutionary biology remained a powerful force throughout his life.

The good and the bad: Social influences on drug abuse. Nathan Pentkowski, Ph.D. Department of Psychology, University of New Mexico. Many years ago in graduate school, upon hearing that I was

teaching an undergraduate social psychology course, Bob made two proclamations: 1) that this was going to be a huge waste of my time, and 2) that social neuroscience was going to be the future of behavioral neuroscience. My fellow graduate students and I laughed, but as usual, Bob was correct. Indeed, teaching that course impeded my research progress, and more importantly, social neuroscience research has since flourished. Bob and Caroline pioneered measuring social behavior as a tool to examine the neural mechanisms underlying numerous human neuropsychiatric disorders, including anxiety, depression, autism and drug addiction. My initial interest in exploring social influences on drug abuse was sparked after reading a seminal paper written by the Blanchards almost 30 years ago that characterized the effects of chronic social subordination stress on alcohol self-administration. In honor of their pioneering work, I will discuss previous research describing the positive and negative effects of social interactions on drug abuse-related behavior in rodent models of addiction. One of Bob's theories on behavior in general has been validated by this research, which suggests that the influence of social interactions on drug abuse-related behavior are situation specific. For instance, when social interactions occur outside of the drug-taking context, prosocial interactions are protective against drug abuse-related behavior, whereas social stressors enhance vulnerability. In contrast, prosocial interactions that occur within the drug-taking context generally enhance vulnerability to drugs of abuse. Future research investigating the neural mechanisms underlying social influences on drug abuse-related behavior will provide valuable information for not only understanding, but also preventing, the initiation of drug use, and for preventing relapse following periods of abstinence.

Channeling Bob Blanchard: Social behavior assays for mouse models of autism. Jacqueline N. Crawley, MIND Institute, Department of Psychiatry and Behavioral Sciences**,** University of California Davis School of Medicine, Sacramento CA. Autism is a neurodevelopmental disorder diagnosed by two classes of behavioral criteria: (a) social interaction and communication deficits and (b) repetitive behaviors with restricted interests. Over 100 risk genes for autism spectrum disorder have been identified over the past decade. Mice with targeted mutations in these many of these risk genes are increasingly available to test hypotheses about genetic causes of autism. With inspiration from Bob and Caroline Blanchard, our laboratory designed mouse social behavioral assays relevant to the types of unusual social interactions that define autism spectrum disorder. Tests include simple automated measures of sociability, and in-depth scoring of reciprocal social interactions, evaluated longitudinally across developmental stages. Communication in mice is assessed by the emission, detection, and responses to olfactory and auditory social cues. Repetitive behaviors are assayed for spontaneous motor stereotypies, repetitive self-grooming and digging, and perseveration during the reversal phase of water maze spatial navigation. Mouse behavioral assays relevant to associated symptoms of autism, including anxiety, hyperactivity, cognitive impairments, hypo- and hyper-reactivity to sensory stimuli, and sleep disruption, provide further insights into genetic substrates of additional phenotypes. Forward and reverse genetic models will be presented, including BTBR T+ Itpr3^{tf}/J, an inbred strain that displays abnormalities on multiple autism-relevant behavioral tasks, *Engrailed2*, a knockout mouse with a haplotype variant associated with autism in multiple independent cohorts, and 16p11.2 deletion, a human syndrome associated with autism. Further, mouse models offer preclinical translational tools to discover therapeutic targets and to evaluate treatment efficacy. We employ lines of mice with the most robust autism-relevant traits for the discovery of effective therapeutic targets. Proof-of-principle results will be presented on hypothesis-driven pharmacological interventions that reversed social deficits in our mouse models.

Restraint stress and social defeat: what they have in common. Newton S. Canteras and Simone C. Motta SC. Departamento de Anatomia, Instituto de Ciências Biomédicas, Universidade de São Paulo. Bob Blanchard was the great inspiration for our studies on the neural basis of social defense. In the present study we compared the hypothalamic pattern of activation between social defeat and physical

restraint stress. As important stress situations, both defeated and immobilized animals presented a substantial Fos increase in the parvicellular part of the paraventricular nucleus, mostly in the region that contains CRH neurons. In addition, socially-defeated animals, but not physically restraint animals, mobilize the elements of the medial hypothalamic conspecific-responsive circuit, also engaged in other forms of social behavior. Of particular interest, both defeated and immobilized animals presented a clear Fos expression increase in specific regions of the lateral hypothalamic area (i.e., juxtaparaventricular and juxtadorsomedial regions) likely to convey septo-hippocampal information encoding the environmental boundary restraint seen in both forms of stress, and the dorsomedial part of the PMd, which seems to work as a key player for the expression of, at least, part of the behavioral responses during both restraint and social defeat stresses. These results point to interesting commonalities between social defeat and physical constraint stress, suggesting, for the first time, a septo-hippocampal – hypothalamic path likely to respond to the environmental boundary restraint that may act as common stressor component for both forms of stress. Moreover, the comparison of the neural circuits mediating physical restraint and social defense revealed a possible path for encoding the entrapment component during the social confront.

Of mice, men, and Bob Blanchard. David Eilam, Department of Zoology, Tel-Aviv University, Israel
In studying how groups are formed and whether there are leaders that set the behavior of the group, we found that in the elementary group-unit of a dyad, each rat travels a greater distance with higher velocity and takes wider turns compared to its lone traveling. Moreover, rats in dyads spend a long time together, share a home base, and usually one of them leads the other when traveling. Rats in triads and quartets first form dyads, and only later gather into triads and quartets. Therefore, the social environment dominates spatial behavior in rats. This was further demonstrated in food-deprived rats that were first trained individually to collected chocolate sprinkles from 16 equispaced locations. When dyads of these rats were then tested together, they were more engaged in traveling together, one as a leader and one as a follower, rather than collecting the chocolate, illustrating a dominance of sociality over hunger. A leader effect in setting the behavior was also illustrated in groups of voles that were attacked by a barn owl, where we found a negative correlation between social status and corticosterone level. This last finding accords with a previous study by Bob and Caroline Blanchard about rats in the “visible burrow system” apparatus, suggesting that individuals with high social rank are less stressed by a life threat. Before the threat, individuals with high social rank display a mid-range behavior, while low-ranked individuals display behaviors at the extremes of the range. After the life-threat, group members converge to the behavior of the leaders and the entire group display more homogenous behavior. The leaders thus act as stabilizers of the group in cutting the extremes and in setting the behavioral code of the group. This study is supported by The Israel Science Foundation (http://www.isf.org.il) grant 230/13.

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This journal publishes original reports in the areas of pharmacology and biochemistry in which the primary emphasis and theoretical context are behavioral. Contributions may involve clinical, preclinical, or basic research.

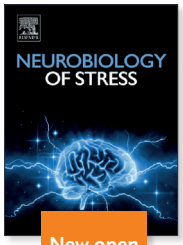
Neuroscience and Biobehavioral Reviews

The journal publishes review articles which are original and significant and deal with all aspects of neuroscience, where the relationship to the study of psychological processes and behavior is clearly established.

Physiology & Behavior

Physiology & Behavior is aimed at the causal physiological mechanisms of behavior and its modulation by environmental factors. The journal invites original reports in the broad area of behavioral and cognitive neuroscience, in which at least one variable is physiological.

Neurobiology of Stress



A multidisciplinary journal for the publication of original research and review articles on basic, translational and clinical research into stress and related disorders. It will focus on the impact of stress on the brain from cellular to behavioral functions and stress-related neuropsychiatric disorders.

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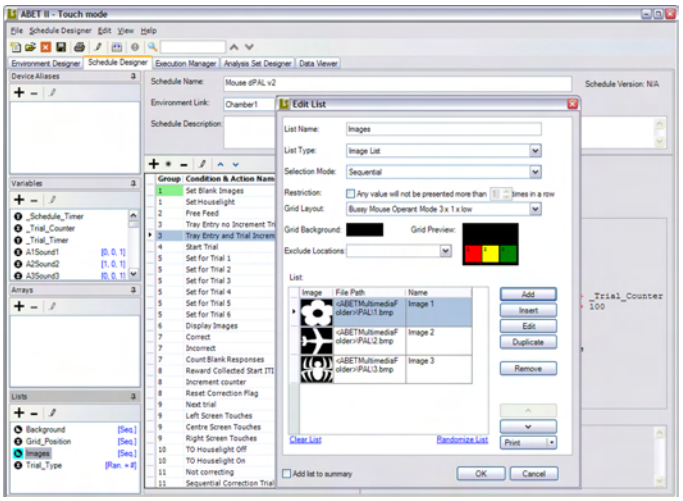
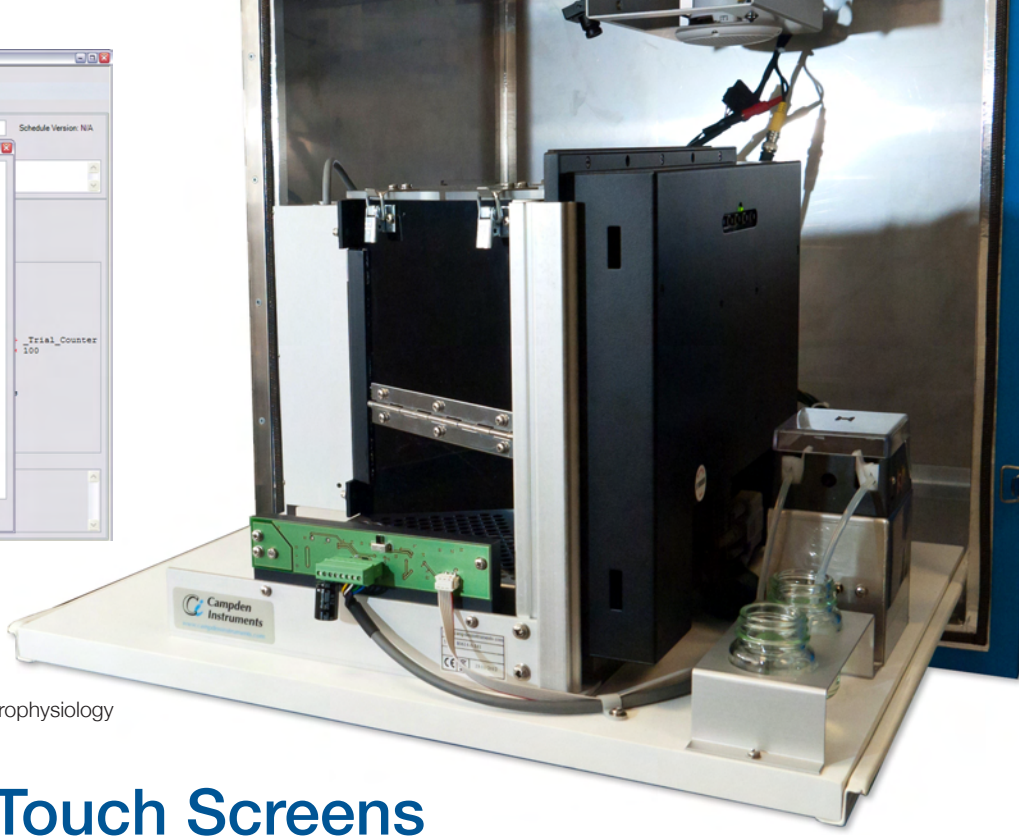


ABET II Touch Software Screenshot



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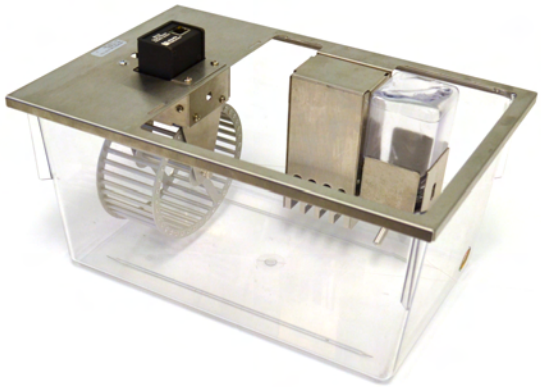

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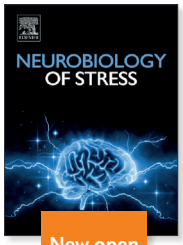

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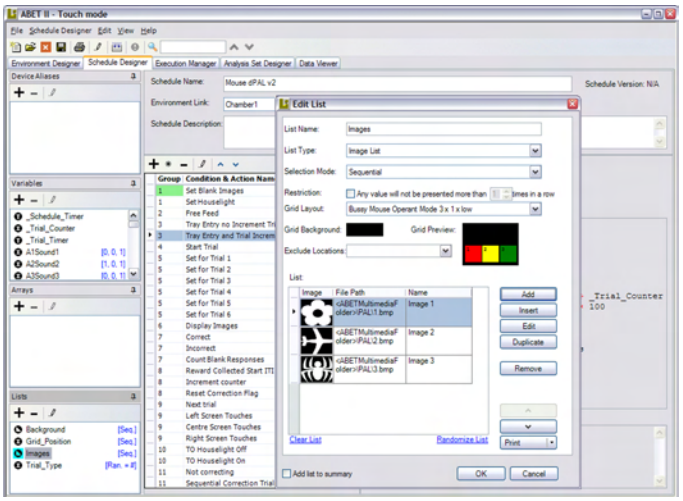

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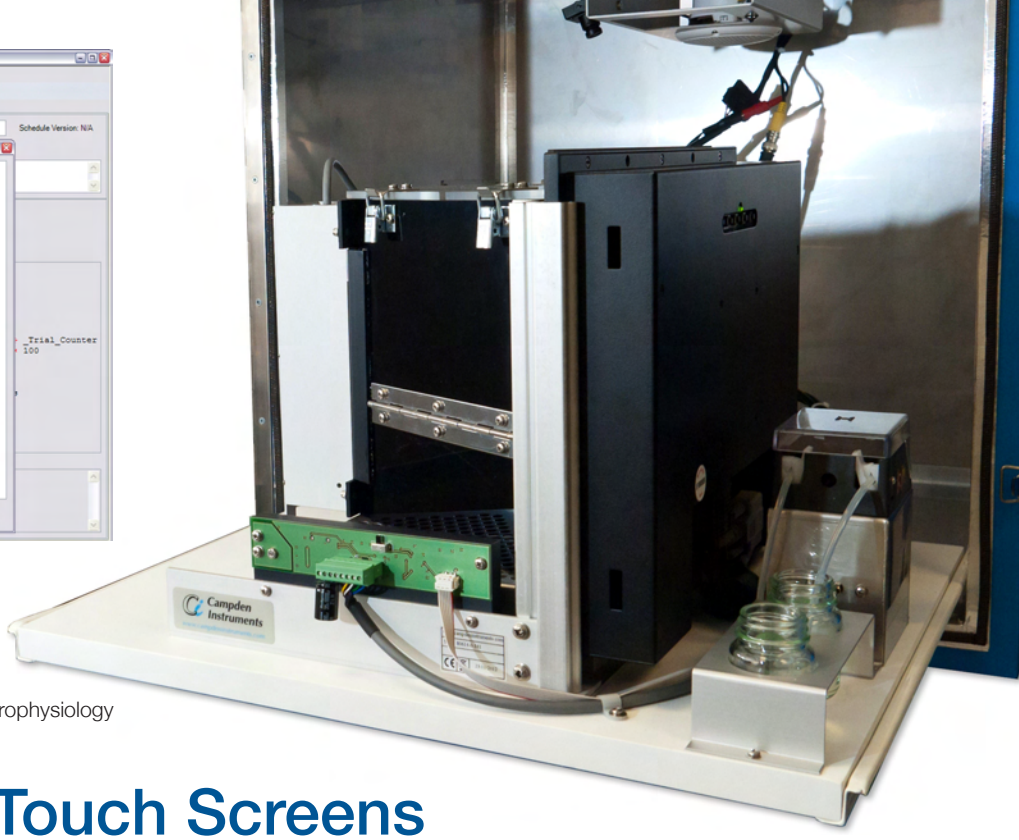

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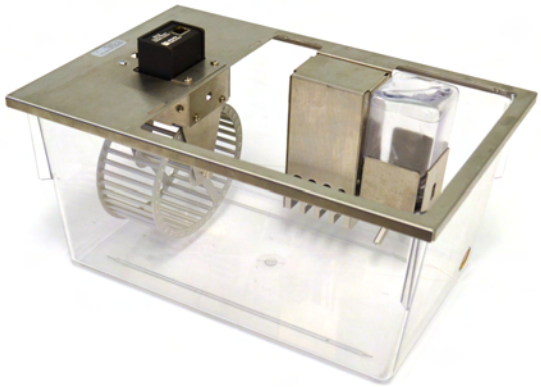

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