IBNS
International Behavioral Neuroscience Society

Annual Meeting Program and Abstracts

Red Rock Resort
Las Vegas, Nevada
June 10-15, 2014

Abstracts of the International Behavioral Neuroscience Society

Volume 23, June 2014

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IBNS CENTRAL OFFICE

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PRESIDENTIAL WELCOME

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http://www.latrobe.edu.au/psy/about/staff/profile?uname=SPKent

Viva Las Vegas! Elvis may have left the building but he's being replaced by 250 behavioural neuroscientists. Somehow I suspect Las Vegas has seen far worse. Las Vegas is a city that needs no introduction. It's internationally renowned for its over the top mega casino-hotel complexes filled not only with gambling opportunities but also fine dining, amazing live shows, and shopping. Our venue, the Red Rock Resort, is off The Strip and looks beautiful enough to keep everyone focussed on the meeting and not the gaming tables.

The last two IBNS meetings have been the largest in our history and this one appears to be another 200+ attendee affair. The Program Committee has organized an exciting set of talks, symposia, and posters. True to our name, our keynote speakers are international and represent 3 different continents and cover a wide range of behavioural neuroscience covering both basic and translational approaches to obesity, depression, psychosis, and bipolar disorder. Once again, we'll be running parallel symposia sessions ensuring there is always stimulating science being presented no matter your interests. Topics include traumatic brain injury, chronic stress, deep brain stimulation, diet and immunity, and sex differences. There is even a symposium dedicated to gambling. Yes, you read that last item correctly.

This year the society has done something new; thanks to you we have raised $1075 to provide local primary school children with bicycle helmets and to raise awareness of traumatic brain injury. I'm proud to be associated with such a philanthropic group of scientists and see this as another way for us to educate the public to the exciting possibilities that lie in our efforts to better understand the brain and its relationship to behaviour.

As always, the core function of IBNS is to encourage research in behavioural 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.

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USA ..... Jared Young

TRAVEL AWARDS

We are pleased to announce the recipients of the IBNS Travel Awards for the 2014 meeting in Las Vegas. 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

Wendy Adams, University of British Columbia, Canada
Davide Amato, University Hospital Erlangen, Germany
Marci Mitchell, Yale University, United States
Caitlin Orsini, University of Florida, United States
Tomasz Schneider, Durham University, United Kingdom
Fiona Zeeb, Centre for Addiction and Mental Health, Canada

Graduate Student Travel Awards

Allison Auchter, University of Texas, United States
Gregory Barord, CUNY Brooklyn College, United States
Michael Barrus, University of British Columbia, Canada
Blanca Sofia Beas, University of Florida College of Medicine, United States
Michael Bowen, University of Sydney, Australia
Xi Chu, University of Tromso, Norway
Caylen Cloutier, University of Western Ontario, Canada
Paul Cocker, University of British Columbia, Canada
Lauren DePoy, Emory University, United States
Kelsy Ervin, University of Guelph, Canada
Julianne Jett, University of Texas Health Science Center, United States
Samantha Mahabir, University of Toronto Mississauga, Canada
Elizabeth Manning, Florey Institute of Neuroscience & Mental Health, Australia
Chantelle Terrillion, University of Maryland, United States
Lucas Watterson, Arizona State University, United States

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The IBNS would like to express our gratitude to the following organizations that have given financial support to the 23rd 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

Jared W. Young, Chair, UCSD, La Jolla, CA, USA
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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/?page=Committees.

PROGRAM

Monday, June 9

9:00-3:00 **Brain Safety Initiative – Education & Training Committee/Local Organizing Committee**

7:00-10:00 **Council Planning Meeting -** *Grand Café*

Tuesday, June 10

11:00-1:00 **Council Meeting** - *Willows*

2:30-4:30 **Student Social** (for students & post-docs) - *Veranda F*

4:30-6:00 **Registration -** *Foyer Cherry Lounge*

6:00-9:00 **Welcome to Vegas Reception -** *Cherry Lounge*
Light hors d'voeres and drinks will be served from 6:00-7:00; cash bar from 7:00-9:00
Join us for an evening of fun and entertainment

Wednesday, June 11

7:30-8:00 **Exhibitor Displays - Coffee/Tea Break** - *Pavilion Ballroom*

8:00-10:00 **Symposia: The importance of the alleviation of negative affective states and cognitive impairments in animal models of nicotine dependence**. Chair: F. Scott Hall – *Charleston AF*

8:00 Investigating the neural basis of nicotine withdrawal-induced attentional deficits. K. Higa, A. Grim, M. Kamenski, J. van Enkhuizen, X. Zhou, R. K. Naviaux, A. Markou, J. W. Young

8:30 Nicotine withdrawal increased anxiety-like behavior and decreased reward responsiveness: Translational measures in rats and humans. A. Markou, X. Li, V. B. Risbrough, A. Der-Avakian

9:00 Genetic, developmental, and receptor level influences on nicotine withdrawal-associated deficits in learning. T. Gould

9:30 Targeting nicotine withdrawal to develop more effective treatments for smoking cessation. M. Shoaib.

8:00-10:00 **Symposia: Brains in the City: Neurobiological effects of urbanization.** Chair: Kelly Lambert – *Charleston BCDE*

8:00 The effects of natural and artificial environments on biomarkers of emotional resilience. K. G. Lambert

8:30 How does the urban environment get under the skin? Examples from urban mental health. S. Galea

9:00 Effects of light pollution on neuroinflammation and mood. R. J. Nelson

9:30 Violence and the city: Biomarkers in children and adults. T. Jovanovic, K. Ressler

10:00-10:20 **Exhibitor Displays - Coffee/Tea Break -** *Pavilion Ballroom*

10:20-10:30 **Presidential Welcome** – Brain Safety Initiative

10:30-11:30 **Keynote Speaker.** Cross-species translational studies of bipolar disorder. M. Geyer – *Charleston BCDE*

11:30-1:00 **Lunch/Networking Break** (meals not provided)

1:00-3:00 **Young Investigator Travel Award Data Blitz** – *Charleston BCDE*

Wendy Adams, University of British Columbia, Canada
Exploring cognitive function in obesity: Assessment of 5-choice serial reaction time task performance in leptin-knockout rats.

Davide Amato, University Hospital Erlangen, Germany
Intra-hippocampal injections of C16 ceramide leads to depressive-like behaviour in mice.

Allison Auchter, University of Texas at Austin, United States
Therapeutic effects of methylene blue on cognitive impairments following chronic cerebral hypoperfusion.

Gregory Barord, CUNY Brooklyn College, United States
The role of environmental cues, their effect on navigational tactics, and its application to the natural ecology of Nautilus.

Michael Barrus, University of British Columbia, Canada
Win-related cues drive risky decision-making on a rodent Gambling Task.

Blanca Beas, University of Florida College of Medicine, United States
GABA(B) receptor signaling and behavioral flexibility in aging.

Michael Bowen, University of Sydney, Australia
Oxytocin acts as a potent ethanol antagonist in vivo and in vitro via non-oxytocin receptor mediated blockade of ethanol enhanced activity at GABAA δ subunit containing receptor interfaces.

Xi Chu, University of Tromso, Norway
Sociosexual behaviors of male rats (Rattus norvegicus) in a seminatural environment.

Caylen Cloutier, University of Western Ontario, Canada
The effects of immune system stimulation on toxin (LiCl)-induced conditioned place avoidance in the female rat.

Paul Cocker, University of British Columbia, Canada
Anterior cingulate cortex inactivations increase reward expectancy on a rodent slot machine task.

Lauren DePoy, Emory University, United States
Mechanisms and reversal of adolescent cocaine-induced habits.

Kelsy Ervin, University of Guelph, Canada
Social learning enhancements may be due to rapid estrogenic action in the hippocampus.

Julianne Jett, University of Texas Health Science Center United States
Noradrenergic dysregulation of glutamate in the mPFC: A potential mechanism for cognitive dysfunction in rats exposed to chronic unpredictable stress.

Samantha Mahabir, University of Toronto Mississauga, Canada
Strain dependent cell death induced by embryonic alcohol exposure in zebrafish.

Elizabeth Manning, The Florey Inst. of Neuroscience & Mental Health, Australia
Long term effects of stress block aversive effects of kappa opioid receptors.

Marci Mitchell, Yale University, United States
A novel inter-temporal choice task.

Caitlin Orsini, University of Florida, United States
Lesions of the basolateral amygdala induce elevated risk-taking in rats.

Tomasz Schneider, University of Oxford, United Kingdom
Enhanced performance in GluA1 knockout mouse in the 5-CSRTT.

Chantelle Terrillion, University of Maryland, Baltimore, United States
Cacna1c haploinsufficiency leads to altered mesolimbic dopamine system function.

Lucas Watterson, Arizona State University, United States
Abuse liability and toxicity of "bath salts" (i.e. synthetic cathinones) as revealed by Intravenous drug self-administration and ex-vivo MRI.

Fiona Zeeb, Centre for Addiction and Mental Health, Canada
Permanent depletion of serotonin increases risky decision-making and impairs acquisition of the rat gambling task.

3:00-3:30 **Exhibitor Displays - Coffee/Tea Break -** *Pavilion Ballroom*

3:30-5:30 **Symposia: That's why they call it gambling: Neural mechanisms regulating risk/reward decision making.** Chair: Stan B. Floresco – *Charleston BCDE*

3:30 What's better for me: Neural circuits mediating subjective decision biases. S. B. Floresco

4:00 No pain no gain: Dopaminergic modulation of risky decision making. B. Setlow

4:30 You got to know when to hold 'em: Prefrontal neural correlates of response inhibition. D. Moorman

5:00 Good money after bad: Using mouse and human gambling tasks to explore why bipolar patients chase the risk. J. van Enkhuizen, B. L. Henry, A. Minassian, W. Perry, M. Milienne-Petiot, K. Higa, M. A. Geyer, J. W. Young

3:30-5:30 **Symposia: Behavioral endpoints in drug discovery: What does the pharmaceutical industry need?** Chair: Sophie Dix – *Charleston AF*

3:30 Where Next? The past, present, and future of behavior in drug discovery. D. McKinzie

4:00 Translatable assays for cognitive research: The use of touchscreens in drug discovery. S. Dix

4:30 Combining *in vivo* electrophysiology and behavior – A circuit based approach to drug discovery. L. Scott

5:00 Imaging behavior: *In vivo* oxygen amperometry as a proxy for BOLD signal in rodents. G. Gilmour

5:30-7:30 **Poster Session 1** – *Pavilion Ballroom*
Light refreshments – bring your drink ticket (one per person); cash bar

1. Effects of methamphetamine and barren housing on allocentric learning and memory in adult rats. A. Gutierrez, R. M. Amos-Kroohs, M. T. Williams, C. V. Vorhees

2. Decreased myelin basic protein expression in the ventromedial prefrontal cortex of adult male rats enhances impulsive choice in a delayed discounting task. S. M. Webb, M. A. McCloskey, D. Maliniak, M. Rangel, T. Alterman, C. Hudson, K. K. Szumlinski.

3. Lesions of anterior and posterior subregions of the pedunculopontine tegmentum differentially affect sensorimotor gating. S. Schmid, J. Robinson.

4. Selective agonism of α3, but not α1 subunit-containing GABAA receptors in the amygdala induces anxiolytic-like effects as measured by elevated plus maze in mice. Y. Gao, S. Heldt

5. Anabolic steroids modulate fatty acid abundance and metabolism in the hippocampus of adolescent rats. M. E. Santigo-Gascot, N. E. Chorna, J. L. Barreto-Estrada

6. Exposure to NMDA receptor antagonists at P7 alters prepulse inhibition at P21 in rats. J. J. Gifford, R. A. Zacharias, S. Kang, C. P. Turner, B. L. Thomas

7. Repeated amphetamine exposure induces behavioral, neurophysiological and molecular alterations of dopaminergic function in the basolateral amygdala. M. Tse

8. Effects of adolescent nicotine exposure on spatial learning and memory in the adult male rat. M. Blose

9. Cyclo-Glycyl-glutamine blockade of the alcohol deprivation effect in P rats. G. E. Resch, J. Lindgren, C. W. Simpson

10. Reactivation of cocaine reward memory engages the Akt/GSK3/mTOR signaling pathway. X. Shi, E. M. Unterwald

11. Sociosexual behaviors of male rats (Rattus norvegicus) in a seminatural environment. X. Chu[TravelAward], A. Ågmo

12. Dose-dependent effects of amphetamine challenge on locomotion following chronic methamphetamine exposure in mice: Divergent quantitative and qualitative effects of BDNF deficiency. E. Manning, A. Halberstadt, M. van den Buuse

13. Preferential activation of immature neurons in the temporal dentate gyrus by cocaine place preference. J. L. Barr, E. M. Unterwald

14. Neuropsychological functioning and emotional disturbance: A comparison amongst mentally retarded and ADHD children. A. Ahsan

15. Interaction of diet and a misaligned circadian rhythm in an animal model of shift work. C. H. Wideman, H. M. Murphy

16. Exercise increases expression of neurotrophic factors in hippocampal microglia of aged mice. A. Littlefield, S. Setti, C. Diaz, E. Guendner, R. Kohman

17. Expression of mutant DISC1 in Purkinje cells affects Purkinje cells morphology and produces cognitive and social abnormalities in adult mice. A. V. Shevelkin, B. N. Abazyan, B. Button, G. L. Rudow, C. A. Ross, J. C. Troncoso, M. V. Pletnikov

18. Ketamine prevents the development of avoidance behavior after social defeat stress in adolescent male mice. S. Nieto, L. Riggs, G. Dayrit, E. Flores, V. Cao, K. Shawhan, B. Cruz, S. Iñiguez

19. Effect of high fat diet consumption on endotoxin-induced cognitive deficits. S. Setti, A. Littlefield, C. Diaz, A. Jones, S. Johnson, R. A. Kohman

20. Therapeutic effects of methylene blue on cognitive impairments following chronic cerebral hypoperfusion. A. Auchter[TravelAward], J. Williams, B. Barksdale, F. Gonzalez-Lima

21. DISC1 mutation and adolescent cannabis exposure interact to produce adult psychopathology. B. Abazyan, S. Abazyan, C. Yang, A. Kamiya, M. Pletnikov

22. Chronic leptin antagonist administration to the VTA increases food intake without altering motivation to obtain either high fat or high sugar pellets: Dissociation between “liking” and “wanting”. P. J. Scarpace, M. Matheny, D. C. Khamiss, J. A. Nwokolo, H. Z. Toklu, N. Tümer, D. Morgan

23. The effects of immune system stimulation on toxin (LiCl)-induced conditioned place avoidance in the female rat. C. J. Cloutier[TravelAward], M. Kavaliers, K. P. Ossenkopp

24. Noradrenergic dysregulation of glutamate in the mPFC: A potential mechanism for cognitive dysfunction in rats exposed to chronic unpredictable stress. J. D. Jett[TravelAward], D. A. Morilak

25. Potential therapeutic target for adult ADHD: D4 receptor agonist (A-412997) improves performance in the 5C-CPT in a rat model of the inattentive subtype of adult ADHD. A. Tomlinson, K. M. Marshall, J. C. Neill

26. Role of nucleus accumbens in generation of 50 kHz vocalizations induced by systemic amphetamine. K. G. Mulvihill, S. M. Brudzynski

27. Anterior cingulate cortex inactivations increase reward expectancy on a rodent slot machine task. P. J. Cocker[TravelAward], J. G. Hosking, C. A. Winstanley

28. Reproduction and maternal experience alter neuroplasticity in the midbrain dorsal raphe. M. A. Holschbach, J. S. Lonstein

29. Differential expression of Fos-family protein in the maternal and non-maternal brain. C. M. Ragan, M. A. Holschbach; A.J. Robison; J. S. Lonstein

30. GABA(B) receptor signaling and behavioral flexibility in aging. B. Beas[TravelAward], C. Banuelos, R. Gilbert, B. Setlow, J. Bizon

31. The role of hippocampal G-protein coupled estrogen receptor in social recognition and object recognition learning in the absence of spatial cues in female mice. J. Lymer, C. Gabor, A. Phan, F. Young-MacDonald, H. Morris, E. Choleris

32. Modulation of male social behaviors by parathyroid hormone 2 receptor expression in the medial amygdala. M. Tsuda, T. Usdin

33. Effects of striatal lesions on reward choice using a multi-box environment. J. M. Ricker, R. Kopchock, J. Hatch, C. Downey, H.C. Cromwell

34. Intermittent access to a cafeteria-type diet affects feeding behavior of female marmoset monkeys. A. C. Borges, R. B. M. Duarte, P. C. B. Bomfim, J. R. Costa, M. Barros

35. Chocolate induces a conditioned-place-preference response in a nonhuman primate. R. B. M. Duarte, E. Patrono, A. C. Borges, S. C. Mitri, A. A. S. César, C. Tomaz, R. Ventura, A. Gasbarri, S. Puglisi-Allegra, M. Barros

36. Differential effects of pharmacological and restraint stress on effort-based decision-making. C. Bryce, S. Floresco

37. Dopamine in the basolateral amygdala modulates choice during risk/reward decision making. J. Larkin, S. Floresco

38. Hippocampal glucocorticoid and mineralocorticoid receptor responses to acute and repeated restraint stress exposure in male and female rats. L. Innala, V. Viau

39. A novel inter-temporal choice task. M. R. Mitchell[TravelAward], N. J. Smith, D. Lee, J. R. Taylor

Thursday, June 12

7:30-8:00 **Exhibitor Displays - Coffee/Tea Break** - *Pavilion Ballroom*

8:00-10:00 **Symposia: Warm feelings, warm thoughts: Thermosensation, emotional behavior, and mental health.** Chair: Christopher A. Lowry – *Charleston AF*

8:00 Disruption in body temperature diurnal rhythms predict stress sensitization. M. Fleshner, R. Thompson

8:30 That warm fuzzy feeling: Warm temperature activates brain serotonergic systems and has antidepressant-like effects in rats. C. A. Lowry

9:00 Warm feelings, interpersonal warmth: Cutaneous heating promotes interpersonal warmth. M. W. Hale

9:30 Warm feelings, warm thoughts: Whole body heating has rapid antidepressant effects in depressed patients. C. L. Raison

8:00-10:00 **Symposia: Chronic stress and brain plasticity: Contrasting mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders.** Chair: Serge Campeau – *Charleston BCDE*

8:00 Adapting to Stress: A Path of Most "Resistance". S. Campeau

8:30 Know when to take your chips off the table – acute stress adaptation begets chronic stress pathology. D. Morilak

9:00 Role of medial prefrontal cortex as modulator and target of stress responses. J. Radley

9:30 Stress and gonadal steroids: Implications for understanding sex differences in responses to homeostatic threat and vulnerability to disease. V. Viau

10:00-10:30 **Exhibitor Displays - Coffee/Tea Break** – *Pavilion Ballroom*

10:30-11:30 **Bench-to-Bedside Lecture.** Coming to our senses: Implications of embodiment for the pathogenesis and treatment of major depression. C. L. Raison – *Charleston BCDE*

11:30-12:15 **Publishing Workshop.** Toby Charkin, Elsevier. Panelists: Stephen Kent, Jared Young, Mikhail Pletnikov – *Charleston AF*

12:30-2:00 **Meet the Professionals** (meals not provided) – *meet in Pavilion Ballroom*

12:15-3:00 **Lunch/Networking Break** (meals not provided)

3:00-3:30 **Exhibitor Displays - Coffee/Tea Break** – *Pavilion Ballroom*

3:30-5:30 **Symposia: The role of CRF and CRF receptor expression in the progression and pathology of major depressive disorder.** Chairs: Marion Rivalan and R. Parrish Waters, Cliff Summers – *Charleston BCDE*

3:30 Sex differences in Corticotropin Releasing Factor 1 Receptors: From molecules to mood. D. Bangasser

4:00 The role of CRF in mediating an individual's risk to social stress-induced psychopathology. S. K. Wood, R. J. Valentino

4:30 Dissecting CRH-controlled Neurocircuitries of Stress and Anxiety. N. Dedic, C. Kühne, K. Gomes, M. Schieven, J. Hartmann, K. V. Wagner, C. Wotjak, D. Refojo, M. V. Schmidt, W. Wurst, J. M. Deussing

5:00 Clinical biomarkers for central CRF overexpression – Identifying the right patient for CRF1 antagonistic treatment. M. Ising, F. Holsboer

3:30-5:30 **Oral Session 1: Addiction** – *Charleston AF*

3:30 The galanin-3 receptor (GALR3) antagonist, SNAP 37889, reduces ethanol consumption in alcohol-preferring mice. K. J. Scheller, B. L. Ash, T. Quach, S. J. Williams, A. J. Lawrence, E. Djouma

3:45 Strain dependent cell death induced by embryonic alcohol exposure in zebrafish. S. Mahabir[TravelAward], D. Chatterjee, R. Gerlai

4:00 ERK phosphorylation of mGluR5 within the BNST regulates alcohol sensitivity in mice. R. R. Campbell, R. S. Waltermire, J. A. Courson, D. I. Greentree, S. G. Quadir, H. McGregor, K. K. Szumlinski

4:15 Methamphetamine exposure combined with HIV-1 disease or gp120 expression: Comparison of learning and executive functions in humans and mice. J. Kesby, R. Heaton, J. Young, A. Umlauf, S. Woods, S. Letendre, A. Markou, I. Grant, S. Semenova

4:30 Sprague Dawley rats show a behavioral predisposition for ethanol consumption or aversion that can be modulated by serotonin. R. K. Vasudeva, L. G. Kirby

4:45 Effects of neonatal maternal separation on behavioral and neural responses to methamphetamine. L. M. Pritchard, E. Hensleigh, M. Pierce, K. AbuAli, S. Lynch, A. Fowler, J. Egan, M. Eby, M. Orlewicz, A. Jager, M. Semmel

5:00 Neuropsychological Influences on Cognitive Training. S. Rabipour, P. Davidson

5:15 Transcranial infrared laser stimulation of cognitive functions. F. Gonzalez-Lima, D. W. Barrett

5:30-7:30 **Poster Session 2**– *Pavilion Ballroom*
Light refreshments – bring your drink ticket (one per person); cash bar

40. The role of hippocampal dopamine D1-type receptors in social learning, feeding behavior and social interactions in male and female mice. R. Matta, A. N. Tiessen, M. M. Kivlenieks, A. M. Meersseman, Y O. Adjei-Afriyie, E. Choleris

41. Prenatal methamphetamine affects neurotransmitter levels in adult ventral hippocampus. R. Slamberova, M. Fujakova, M. Vrajova, J. Sirova, P. Kacer, D. Ripova, J. Horacek

42. Abuse liability and toxicity of “bath salts” (i.e. synthetic cathinones) as revealed by Intravenous drug self-administration and ex-vivo MRI. L. Watterson[Travel Award], M. F. Olive

43. Toluene overexpsoure provokes alterations in memory and hippocampal brain structure of adolescent and adult rats. M. Zhvania, N. Japaridze, M. Dashniani, M. Burjanadze, T. Bikashvili, N. Pochkhidze

44. The alterations provoked by toluene over exposure on locomotor activity, behavior in maze and hippocampal structure in adolescent and adult rats. M. Zhvania, N. Japaridze, M. Dashniani, M. Burjanadze, T. Bikashvili, N. Pochkhidze

45. Incubation of cocaine-craving relates to a sensitization of cue-mediated glutamate over-flow in the vmPFC. C. B. Shin, M. M. Serchia, J. R. Shahin, A. E. Agaronova, K. K. Szumlinski

46. The role of environmental cues, their effect on navigational tactics, and its application to the natural ecology of Nautilus. G. J. Barord[TravelAward], R. Derman, C. Ju, T. Vargas, J. Basil

47. Permanent depletion of serotonin increases risky decision-making and impairs acquisition of the rat gambling task. F.D. Zeeb[TravelAward], C.A. Winstanley, P.J. Fletcher

48. Nucleus accumbens glutamate bidirectionally regulates methamphetamine addiction vulnerability. L. M. Schwartz, K. D. Lominac, M. G. Wroten, P. N. Ruiz, B. W. Miller, J. Holloway, K. O. Travis, G. Rajasekar, D. Maliniak, A. B. Thompson, L. E. Urman, H. Barrett, T. J. Phillips, K. K. Szumlinski

49. Zebrafish and conditioned place preference: A translational model of drug addiction. A. Collier, K. Khan, E. Caramillo, D. Echevarria

50. Enhanced fear conditioning in mice exposed to perinatal ketamine. A. Khan, M. Behrens, B. Risbrough, S. Powell

51. Phosphodiesterase 1B knockout mice are resistant to the induction of depression-like behavior. J. R. Hufgard, M. R. Skelton, M. T. Williams, C. V. Vorhees

52. Cacna1c haploinsufficiency leads to altered mesolimbic dopamine system function. C. Terrillion[TravelAward], M. Arad, D. Dao, R. Cachope, J. Cheer, T. Gould

53. Chronic social stress during puberty alters appetitive male sexual behavior and neural metabolic activity. C. Bastida, F. Puga, F. Gonzalez-Lima, K. Jennings, J. Wommack, Y. Delville

54. Motivation orientation and propensity for Flow among elite American football players. D. Vaughn

55. The antipsychotic drug haloperidol reduces the efficacy of environmental enrichment after traumatic brain injury. J. B. Leary, M. J. LaPorte, E. A. Ogunsanya, A. M. Greene, K. E. Free, J. P. Cheng, C. O. Bondi, A. E. Kline

56. Environmental enrichment as a preclinical model of neurorehabilitation. V. V. Mattiola, J. B. Leary, A. M. Greene, J. P. Cheng, C. M. Monaco, C. O. Bondi, A. E. Kline

57. Exploring cognitive function in obesity: Assessment of 5-choice serial reaction time task performance in leptin-knockout rats. W. Adams[TravelAward], A. D'souza, J. Sussman, T. Kieffer, C. Winstanley

58. Intra-hippocampal injections of C16 ceramide leads to depressive-like behaviour in mice. D. Amato[TravelAward], M. Reichel, E. Gulbins, J. Kornhuber, C. P. Müller

59. Extended access to cocaine produces distinct changes in Homer2 and NPAS4 gene expression. K. Ploense, D. Baker-Andresen, X. Li, Y. Sun, T. Bredy, T. Kippin

60. Oxytocin acts as a potent ethanol antagonist in vivo and in vitro via non-oxytocin receptor mediated blockade of ethanol enhanced activity at GABAA ð subunit containing receptor interfaces. M. T. Bowen[TravelAward], S. Peters, N. Absalom, M. Collins (Chebib), I. D. Neumann, I. S. McGregor

61. Differential involvement of hypothalamus-pituitary-adrenal-axis activity in the effects of enhanced 2-arachidonoylglycerol signaling on responses to social and non-social challenges. M. Aliczki, D. Zelena, E. Mikics, Z. K. Varga, O. Pinter, N. Venczkone Bakos, J. Haller

62. Effects of chronic unpredictable restraint stress and a post-stress recovery period on spatial learning in male and female rats. J. B. Ortiz, A. N. Campbell, A. N. Hoffman, S. B. Taylor, L. R. Lucas, C. D. Conrad

63. Prefrontal GABA-blockade and decision making. P. T. Piantadosi, S. Khayambashi, A. Cywinska, M. Schluter, S. Floresco

64. Mechanisms and reversal of adolescent cocaine-induced habits. L. M. DePoy[TravelAward], S. L. Gourley

65. Whole-body prepulse inhibition protocol for testing in capuchin monkeys: Preliminary findings on superior colliculus lesion. P. Saletti, R. Maior, T. Hori, H. Nishijo, C. Tomaz

66. Neuropsychological functioning in children with sickle cell disease and pica. N. S. David, E. T. O'Callaghan, J. I. Gold

67. Screening for autism in preterm children with birth weights less than 1500 g. I. Dudova, M. Kasparova, D. Markova, J. Zemankova, S. Beranova, T. Urbanek, M. Hrdlicka

68. Memory impairment of APP-transgenic mice in pre-amyloid stage is linked to a reduced support of formation of neuronal processes in the hippocampal neurogenic niche. B. Mazur-Kolecka, G. Lafauci, R. Rubenstein, W. Kaczmarski, J. Frackowiak

69. The impact of brain levels of monomeric A and Cdk5 activation on learning and memory impairment in mouse models of brain amyloidosis-beta. J. Frackowiak, B. Ranasinghe, G. Lafauci, R. Rubenstein, R. Kolecki, W. Kaczmarski, B. Mazur-Kolecka

70. The efficacy of cold facial immersion and the diving response in treating panic disorderr. P. Kyriakoulis, M. Kyrios, D. liley, M. Schier

71. Predator odor- induced fear: A behavioral characterization and neural substrate analysis. K. Wernecke, D. Vincenz, S. Storsberg, J. Goldschmidt, W. D'Hanis, M. Fendt

72. Spatial long-term memory and modulation of NMDA receptor subunit expression in medial septal immunolesioned rats. T. Naneishvili, M. Dashniani, M. Burjanadze, N. Chkhikvishvili, G. Beselia, M. Chighladze

73. Nucleus accumbens response to palatable food positively correlates to subjective food craving score in overweight subjects. Y. Nakamura, D. M. Small

74. Impaired attentional selectivity in rats with subthalamic nucleus lesions. S. Xia, D. Tait, V. Brown

75. Long term effects of stress block aversive effects of kappa opioid receptors. A. Laman-Maharg, K. L. Campi, C. E. Manning[TravelAward], M. Z. McMackin, C. F. Robles, E. Y. Takahashi, B. C. Trainor

76. Acute inflammatory pain and DNA methyltransferases. E. Abzianidze, E. Kvaratskhelia, T. Tkemaladze, G. Gurtskaia, M. Nebieridze, L. Nozadze, M. G. Tsagareli

77. Repeated treatment with the D1 agonist SKF81297 yields impairment of object memory in rats. H. Taukulis, J. Ilkay

Friday, June 13

7:30-8:00 **Exhibitor Displays - Coffee/Tea Break** - *Pavilion Ballroom*

8:00-10:00 **Symposia: Current advances in animal models of neurodevelopmental disorder**s. Chair: Mu Yang – *Charleston BCDE*

8:00 Advanced assays for therapeutic development in models of autism. J. L. Silverman, M. C. Pride, J. E. Hayes, J. N. Crawley

8:30 Alterations in cortical firing and executive control deficits after prenatal alcohol exposure. K. Marquardt, R. Sigdel, J. L. Brigman

9:00 A nonhuman primate model of maternal immune activation. M. D. Bauman

9:30 Engineered deafness reveals that mouse courtship vocalizations do not require auditory experience. E. Mahrt, D. Perkel, L. Tong, E. Rubel, C. Portfors

8:00-10:00 **Symposia: Deep brain stimulation of the basal ganglia nuclei: Animal and human studies.** Chair: Claudio Da Cunha – *Charleston AF*

8:00 The role of the basal ganglia in action-selection. C. Da Cunha

8:30 Simultaneous neurochemical sensing, stimulation, and fMRI studies using WINCS harmoni during deep brain stimulation. K. H. Lee, A. J. Bieber, K. E. Bennet

9:00 Subsecond release of striatal DA after stimulation of subthalamic nucleus: Animal and human studies. C. D. Blaha

9:30 Mapping the functional neural network of deep brain stimulation using fMRI. P. Hoon-Ki Min

10:00-10:30 **Exhibitor Displays - Coffee/Tea Break -** *Pavilion Ballroom*

10:30-11:30 **Keynote Speaker.** Closing the translational gap between mutant mouse models and the clinical reality of psychotic illness. J. L. Waddington – *Charleston BCDE*

11:30-1:00 **Lunch/Networking Break** (meals not provided)

1:00-2:45 **Oral Session 2. Disease** – *Charleston BCDE*

1:00 Effects of Antalarmin on hippocampal pCREB expression and characterisation of sociability and social memory in male rats following global cerebral ischemia. P. B. de la Tremblaye, N. N. Linares, H. Plamondon

1:15 Npas4 regulates vulnerability to stress during adolescence. L. Coutellier

1:30 External auditory perception and auditory hallucinations in schizophrenia. T. Ikuta, P. DeRosse, K. H Karlsgodt, P. R. Szeszko, A. K. Malhotra

1:45 Preclinical evaluation of the fast acting antidepressant potential of dextromethorphan: Involvement of AMPA and sigma receptors. R. Matsumoto, L. Nguyen

2:00 Beneficial effects of intranasal NPY and HS014 in preventing PTSD related symptomology: Comparative study. E. Sabban, L. Serova, M. Laukova, L. Alaluf

2:15 Extracellular signal-regulated kinase-2 regulates adult functional responsivity to stressful situations induced by Prozac exposure during adolescence. S. Iñiguez, L. Riggs, S. Nieto, G. Dayrit, B. Warren, E. Nestler, C. Bolaños-Guzman

2:30 Widespread cortical α-ERD companying visual oddball target stimuli is frequency but non-modality specific. W. Peng, Y. Hu

1:00-2:45 **Oral Session 3: Mechanisms** – *Charleston AF*

1:00 Insular activation during reward anticipation reflects duration of illness in abstinent pathological gamblers. K. Tsurumi, R. Kawada, N. Yokoyama, T. Murai, H. Takahashi

1:15 Neural correlates of social interaction during exposure to an acute stressor: Companion identity matters. T. A. R. Weinstein, S. R. Cherry, K. L. Bales

1:30 Lesions of the basolateral amygdala induce elevated risk-taking in rats. C. A. Orsini[TravelAward], R. Trotta, J. L. Bizon, B. Setlow

1:45 Effect of l-glutamate application in the gut and preoptic area on thermoregulation in rats. T. Sengupta, A. K. Jaryal, H. N. Mallick

2:00 Enhanced performance in GluA1 knockout mouse in the 5-CSRTT. T. Schneider[TravelAward], D. Bannerman

2:15 Eating, drinking and sleeping: The role of 5-HT1A receptor in the serotonin-mediated dipsogenic and hypnogenic responses in pigeons (Columba lívia). T. S. Dos Santos, J. Krueger, F. F. Melleu, A. Poli, C. Herold, O. Güntürkün, J. Marino-Neto

2:30 Lesions of Area 8 impair visual conditional selection but not monitoring in working memory. M. Petrides

2:45-3:30 **Exhibitor Displays - Coffee/Tea Break** – *Pavilion Ballroom*

3:30-5:30 **Symposia: Neural mechanism of regulation and disruption of motivational behaviors.** Chairs: Hidehiko Takahashi, Christelle Baunez – *Charleston BCDE*

3:30 Ventral striatal contributions to performance under pressure. V. S. Chib

4:00 Molecular neuroimaging on risk assesment: Beyond dopamine. H. Takahashi

4:30 The monoamine system in monetary incentives. M. Yamada

5:00 The role of the subthalamic nucleus in impulse control disorders. C. Baunez

3:30-5:30 **Symposia: Scents that matter – from olfactory stimuli to genes, behaviors and beyond**. Chairs: M. Fendt, Y. Kiyokawa – *Charleston AF*

3:30 A juvenile mouse pheromone controls adult social behavior. S. Liberles

4:00 An alarm pheromone in rats. Y. Kiyokawa, H. Inagaki, Y. Takeuchi, Y. Mori

4:30 Detection and internal representation of Mup proteins and other predator-derived odors by the vomeronasal system in mice. F. Papes, V. Carvalho, T. Nakahara, M. Souza

5:00 Neural correlates of carnivore urine-induced fear. M. Fendt, K. Wernecke, D. L. Vincenz, S. Storsberg, W. D'Hanis, J. Goldschmidt

5:30-7:30 **Poster Session 3**– *Pavilion Ballroom*
Light refreshments – bring your drink ticket (one per person); cash bar

78. Development of tolerance to ethanol and pentobarbital by the Myers' high ethanol preferring (mHEP) rat allowed to freely consume solutions of ethanol. B. A. McMillen, S. N. Barry, Z. A. Cormier, S. L. Hendricks, E. N. Shirley, H. L. Williams

79. Early methylphenidate exposure alters morphine-mediated antinociception in neonatal 6-OHDA lesioned female rats. G. J. Kaplan, J. M. Valentine, J. Celmer, C. A. Crawford

80. Dietary supplementations as neuroprotective therapies in a rotenone model of Parkinson's disease in mice. I. Zaki, M. Salama, M. El-gamal, Y. Youssef, H. El-Gamal, H. Osama, M. Sobh

81. Parental behavior and the stress response in new world monkeys: A comparative approach. E. Kirk, M. Eckles, T. Landis, S. Evans, K. G. Lambert, M. Bardi

82. Serotonin in the ventral hippocampus modulates anxiety-like behavior during amphetamine withdrawal. J. L. Scholl, W. Tu, A. Cook, M. Mears, M. J. Watt, K. J. Renner, G. L. Forster

83. Coping profiles, emotional resilience and corticosteroid receptors in male rats: A preliminary analysis. B. Thompson, E. Kirk, A. Hazelgrove, M. Bardi, K. Lambert

84. Involvement of dopaminergic mechanisms in antidepressant activity of leptin in mice. R. Cordeiro, V. Tomaz, C. Medeiros, D. Macêdo, A. Carvalho

85. Reduced social behavior and heightened anxiety in 5HTT knockout Mice. M. McBratney, C. Gibson, B. Miranda, J. Lugo, L. A. Martin

86. Effects of social environment on motor and spatial behavior in rats exposed to moderate levels of ethanol or saccharine during gestation. C. M. Magcalas, C. I. Rodriguez, D. Barto, J. P. Rice, B. C. Fink, C. W. Bird, S. Davies, D. D. Savage, D. A. Hamilton

87. The role of PACAP in motivationa effects of nicotine. P. Singh, A. Tseng, A. Hamid, P. Marquez, A. Khisravan Ahoura, K. Lutfy

88. The effects of wheel running exercise on opioid withdrawal-induced conditioned place aversion in mice. K. Wihbey, C. J. Heyser

89. The role of opioids in the reinforcing actions of sugar. A. Khosravan Ahoura, A. Tseng, A. Hamid, P. Singh, P. Marquez, K. Lutfy

90. Social learning enhancements may be due to rapid estrogenic action in the hippocampus. K. Ervin[TravelAward], A. Moore, K. Sinclair, E. Choleris

91. MDMA enhances the extinction of cued fear memory in mice. M. Young, L. Howell

92. Deep brain stimulation in an animal model of schizophrenia: Treatment and prevention. L. Bikovski, I. Weiner

93. Enrichment improves responses to anxiogenic stimuli and modifies dendritic morphology of striatal and hypothalamic neurons in trait anxiety rats. S. T. Donaldson, R. Ravenelle, R. Lott, E. Gildersleeve, P. Bharadwaj, J. H. Park

94. Neuronal circuits underlying transfer of remote emotional information in mice. K. Meyza, T. Nikołajew, K. Kondrakiewicz, J. Sadowska, E. Knapska

95. Win-related cues drive risky decision-making on a rodent Gambling Task. M. M. Barrus[TravelAward], C. A. Winstanley

96. Chronic LPS-induced inflammatory response in a diabetic model of Alzheimer's Disease. A. S. Murtishaw, C. F. Heaney, M. M. Bolton, J. W. Kinney

97. Acute cocaine administration decreases advantageous decision-making but does not affect impulsive action as measured by a rodent gambling task. J-M. N. Ferland, M. Tremblay, W. K. Adams, C. A. Winstanley

98. Prefrontal GABA modulation of working memory processes. M. L. Auger, S. B. Floresco

99. Maternal peri-conceptional cortisol and HPA axis activity in pre-pubertal children. C. Barha, K. Salvante, J. Blais, H. Ma, L. Zeng, P. Nepomnaschy

100. Treating psychotic patients with agonist opioid therapy and atypical antipsychotics. M. C. Pieri, A. C. Comaschi

101. Investigation of anxiety, neuronal injury, and vGluT2 and CRH expression following pre-ischemic administration of cannabinoid receptor 1 antagonist, AM251, in male rats. I. Azogu, M. Dunbar, P. Barra de la Tremblaye, H. Plamondon

102. Unraveling the role of GABA-B receptors on attentional performance, impulsivity and compulsivity. S. Vlachou, A. Campos, K. Kaczanowska, M. G. Finn, A. Markou

103. Effects of permethrin on the acoustic startle response in adult male Sprague-Dawley rats. C. V. Vorhees, T. Osimitz, L. Sheets, D. Minnema, M. Brooks, D. Gammon, M. T. Williams

104. Effects of running wheel pre-exposure on subsequent performance on three motor tasks. K. F. J. Happel, K. Klein-Randall, S. J. Larson

105. Explorations of creative problem-solving and social responses in free-ranging raccoons: A potential role of von Economo neurons? T. Landis, M. Bardi, M. Hyer, A. Rzucidlo, K. Lambert

106. Chronic hypobaric hypoxia exposure causes memory impairment and modulates hippocampal synaptic strength: Enriched environment as a therapeutic approach. V. Jain, D. Prasad, G. Ilavazhagan, S. Bala Singh

107. Sex differences in a rat model of risky decision making. K. G. Shimp, C. A. Orsini, R. J. Gilbert, M. Willis, J. L. Bizon, B. Setlow

108. The role of dopamine in the active threat responding. C. C. De Oliveira, M. C. de Castro, F. V. Gouveia, M. D. J. Seno, L. T. C. dos Santos, G. Antunes, E. T. Fonoff, M. J. Teixeira, J. P. Otoch, R. C. R. Martinez

109. Effects of the antidepressant sertraline given during pregnancy on the dam and the offspring. S. Brummelte, F. A. Shoubah, J. M. Kott, S. M. Mooney-Leber

110. Activation of basal forebrain GABAergic projection neurons alters mPFC-mediated working memory performance in young F344 rats. C. Bañuelos, B. Setlow, J. L. Bizon

111. Chronic stress enhanced fear memories are associated with increased amygdala zif268 mRNA expression and are resistant to reconsolidation in an animal model of post traumatic stress disorder. A. N. Hoffman, A. Parga, L. R. Watterson, P. R. Paode, E. M. Nikulina, R. P. Hammer, Jr., C. D. Conrad

112. Time course analysis of behavioral heterogeneity in MRL/MpJ lupus-prone and control mice. L. Shiue, C. Quinlan, E. Quincer, S. Larson, J. Reber, K. Strand

113. Relationship of serum complement component C3 with autoimmunity-associated behavior in the MRL/lpr model. L. Shiue, C. Quinlan, A. Franz, K. Strand

114. Effects of Chronic Treatment of Corticosterone on Physiological Responses. D. Ortolani, M. Donovan, J. Vargas, E. Layco, G. Onnis, C. Hillar, R. C. SpadariL. H. Tecott

115. Improving undergraduate students' knowledge of neuroscience principles and research methods through structured didactics that complement mentored research training. L. A. Rabin, D. J. Walder, L. Ospina, J. K. Flynn, S. Y. Chi, T. R. Adams. Department of Psychology, Brooklyn College of The City University of New York

Saturday, June 14

7:30-8:00 **Exhibitor Displays - Coffee/Tea Break** - *Pavilion Ballroom*

8:00-10:00 **Symposia: Reproductive experiential regulation of cognitive and emotional resilience.** Chair: Craig H. Kinsley – *Charleston AF*

8:00 Chronic intranasal oxytocin: Long-term effects of a reproductive hormone on behavior and neural systems. K. Bales

8:30 Catch me if you can: Reproductive experience enhances foraging skills in owl monkeys. M. Bardi

9:00 Pregnancy/reproductive experience: A neuro-developmental epoch takes its place alongside sexual differentiation and puberty. C. Kinsley

9:30 Epigenetic regulation of maternal learning. D. Stolzenberg

8:00-10:00 **Symposia: Diet, behaviour, and immunity across the lifespan.** Chair: Stephen Kent – *Charleston BCDE*

8:00 Diet affects executive function: Effects across the lifespan. T. M. Reyes

8:24 The role of microglia in perinatal diet's programming effects on neuroimmune function. L. Sominsky, S. J. Spencer

8:48 Mum's the word: Understanding the role of maternal inflammation in elevating the risk of offspring neuroendocrine disorders. C. Jasoni, D. Kim, T. Sanders

9:12 The interleukin 18 system in the central regulation of feeding. B. Conti

9:36 Calorie restriction attenuates lipopolysaccharide-induced microglial activation in discrete regions of the hypothalamus. M. W. Hale, M. E. Radler, S. Kent

10:00-10:30 **Exhibitor Displays - Coffee/Tea Break** – *Pavilion Ballroom*

10:30 -11:30 **Presidential Lecture**: Food on the brain – Why is obesity a 21st century problem? M. J. Morris – *Charleston BCDE*

11:30-3:00 **Lunch/Networking Break** (meals not provided)

3:00-3:30 **Coffee/Tea Break** – *Pavilion Ballroom*

3:30-5:30 **Symposia: Sex-differences in developmental psychopathologies: An animal model perspective.** Chair: I. Weiner – *Charleston AF*

3:30 Sex-specific behavioral and molecular deficits in ‘two hit’ models of developmental stress: Role of brain-derived neurotrophic factor. M. Van den Buuse, M. Klug, R. Hill

4:00 Sexually dimorphic and developmental effects of maternal separation on prefrontal cortex, behavior and inflammation in rats. H. C. Brenhouse, F. H. Holland, N. Golan, T. Backus

4:30 Immune activation in lactating mothers produces long-term structural brain and behavioral abnormalities that are distinct in male and female sucklings: A novel neurodevelopmental model of sex-biased psychopathology. I. Weiner

5:00 Early-life modulation of Cav1.2 induces sex-specific resiliency to depression. M. Arad, J. M. Bowers, M. M. McCarthy, T. D. Gould

3:30-5:30 **Symposia: Traumatic brain injury: Laboratory and clinical perspectives.** Chairs: Anthony E. Kline, University of Pittsburgh, USA; Corina O. Bondi, University of Pittsburgh, USA – *Charleston BCDE*

3:30 Contemporary Laboratory Models of Traumatic Brain Injury. C. E. Dixon

3:54 Social behavior after injury to the developing brain. B. D. Semple, P. N. Sam, K. Gimlin, A. K. Schenk, L. J. Noble-Haeusslein

4:18 Old dog, new tricks: The attentional set-shifting test as a novel cognitive behavioral task after controlled cortical impact injury. C. O. Bondi

4:42 Standard vs. enriched housing after traumatic brain injury: When less is not more. A. E. Kline

5:06 Fact or fiction: An evidence-based approach to sports-related concussion. C. C. Giza

5:30-6:00 **Business Meeting** – Open to all Members – *Charleston BCDE*

6:30-1:00 **Awards Banquet –** Pavilion Ballroom - *bring your drink ticket (one per person)*
The evening will start with a reception/cash bar followed by award presentations, dinner and dancing. Prizes for the best "Vegas" costume. This fun event is a great way to end a very intensive and educational scientific meeting! What is Las Vegas style?? We will leave that up to you (Elvis, Marilyn, tourist or dressed in your finest formal wear--putting on the ritz/glitz)--prizes for best costumes! Elvis look a-likes welcome!

Sunday, June 15

Departures

Wednesday, June 11

8:00-10:00 **Symposia: The importance of the alleviation of negative affective states and cognitive impairments in animal models of nicotine dependence**. Chair: F. Scott Hall

Investigating the neural basis of nicotine withdrawal-induced attentional deficits. K. Higa1, A. Grim1, M. Kamenski1, J. van Enkhuizen1, X. Zhou1,2, RK. Naviaux1, A. Markou1, JW. Young1,2 1 Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804 2 Research Service, VA San Diego Healthcare System, San Diego, CA. Background: Smoking remains the leading cause of preventable death in the United States and is a huge drain on economic resources. During attempts to quit smoking, cognitive dysfunction predicts relapse. Therefore, improving cognition during withdrawal is a key target in aiding quit attempts. Models investigating the mechanisms underlying nicotine withdrawal-induced cognitive deficits are rare however, particularly in tasks relevant to human cognitive testing. Given nicotinic links to attention - and withdrawal-induced inattention - we explored the mechanisms underlying nicotine withdrawal-induced inattention. The alpha7 nicotinic acetylcholine receptor (nAChR) is a major target of nicotine in the brain. We assessed whether nicotine withdrawal-induced inattention would be seen in alpha7 nAChR knockout (KO), heterozygous (HT), and wildtype (WT) littermate mice performing the mouse 5-choice continuous performance test (5C-CPT). Methods: Mutant mice were trained in the 5C-CPT, counter-balanced into three groups, then implanted with osmotic minipumps filled with saline or nicotine (14 or 40 mg/kg/day). After 28 days, the minipumps were removed and 5C-CPT performance challenged 4 hrs later. Results: Withdrawal from nicotine impaired attention in the 5C-CPT ($F(2,54)=3.5$, $p<0.05$). While a trend effect of genotype was observed ($F(2,54)=3.0$, $p=0.066$), no interaction between genotype and treatment was observed ($F<1$, ns). WT mice exhibited better attention than HT and KO mice ($p<0.05$). Both doses affected performance during withdrawal but only the highest dose was lower than vehicle ($p<0.05$). Withdrawal-induced impaired attention was driven by response disinhibition ($F(2,54)=3.5$, $p<0.05$), with higher false alarm rates during withdrawal at the highest dose ($p<0.05$). Conclusion: Withdrawal from chronic nicotine treatment impaired attentional performance in the mouse 5C-CPT irrespective of alpha7 nAChR level. The impaired attentional performance was primarily due to response disinhibition, while withdrawal did not affect bias. Similar attentional deficits have been observed in smoking withdrawal humans in the 5C-CPT. Hence, the alpha7 nAChR likely does not play a role in the attentional deficits that occur during withdrawal.

Nicotine withdrawal increased anxiety-like behavior and decreased reward responsiveness: translational measures in rats and humans. Athina Markou, Xia Li, Victoria B Risbrough and Andre Der-Avakian. Affective symptoms of nicotine withdrawal, such as anxiety and reward deficits, are hypothesized to be important contributors to relapse to tobacco smoking in humans. Characterization of such affective signs of nicotine withdrawal in rats, using translational measures from human behavioral laboratory procedures, facilitates investigation of the neurobiological substrates of these phenomena, and identification of targets for medications to treat nicotine withdrawal and prevent relapse in humans. Spontaneous nicotine withdrawal potentiated a stress-like response to anxiogenic stimuli in the light-enhanced startle (LES) procedure that assesses unconditioned fear responding, and the fear-potentiated startle (FPS) procedure that assesses conditioned fear responses. Interestingly, spontaneous nicotine withdrawal robustly increased startle reactivity during cued fear, but had no effect on context fear, in the FPS procedure. Furthermore, spontaneous nicotine withdrawal diminished reward responsiveness in rats and humans (i.e., the propensity to modulate behavior as a function of prior reinforcement experience) in the response-bias probabilistic reward task, a translational task developed originally for humans and recently adapted for use in rats. Conversely, acute nicotine administration dose-dependently increased reward responsiveness in rats previously exposed to chronic nicotine, but not in rats exposed to chronic saline. In conclusion, these findings from translational procedures in rats indicate that early nicotine withdrawal is characterized by increased conditioned and unconditioned fear anxiety-like responses, and diminished reward responsiveness. Thus, human smokers may exhibit high rates of relapse during early

abstinence to avoid the aversive negative affective aspects of nicotine withdrawal. By contrast, protracted withdrawal was characterized by increased nicotine-induced responsiveness to rewards that may increase the likelihood of relapse to tobacco smoking by amplifying the positive affective effects of acute nicotine.

Genetic, developmental, and receptor level influences on nicotine withdrawal-associated deficits in learning. Gould, T. Temple University. One of the predominant symptoms smokers experience during quit attempts is changes in cognition. In fact, deficits in cognitive function predict relapse. In the clinical population there is variability in what withdrawal symptoms are expressed across individuals and in the magnitude of the symptoms. Understanding what factors contribute to variability in the expression of cognitive withdrawal symptoms will aid in developing better treatments for nicotine addiction. In mice, withdrawal from chronic nicotine disrupts hippocampus-dependent learning. This presentation will explore the role of age at the time of chronic exposure on the development of nicotine withdrawal deficits in hippocampus dependent learning, the influence of genetic background on expression of nicotine withdrawal deficits in hippocampus dependent learning, and changes in nicotinic acetylcholinergic receptor (nAChR) function that may contribute to nicotine withdrawal deficits in hippocampus-dependent learning. Data suggest that upregulation of high affinity α4β2 nAChRs in the dorsal hippocampus is related to expression of nicotine withdrawal deficits in learning. Furthermore, younger adolescent mice appear less sensitive to effects of nicotine withdrawal on hippocampus-dependent learning and showed less nAChR upregulation but yet were more sensitive to long-term effects of nicotine exposure during adolescence on adult learning. In addition, the genetic background of mice impacts the susceptibility to the effects of nicotine withdrawal on learning and genetic alterations of β2 also impacts susceptibility. Together, these data highlight the importance of considering the multifaceted factors that contribute to development of nicotine addiction.

Targeting nicotine withdrawal to develop more effective treatments for smoking cessation.

8:00-10:00 **Symposia: Brains in the City: Neurobiological effects of urbanization.** Chair: Kelly Lambert

The Effects of Natural and Artificial Environments on Biomarkers of Emotional Resilience. Kelly G. Lambert, Dept. of Psychology, Randolph-Macon College, Ashland VA 23005 USA. The classic enriched environment studies highlighted the importance of the specific characteristics of an animal's environment on various neurobiological variables (Rosenzweig, et al., 1962). Subsequent research has confirmed these initial observations—with rats housed in enriched environments exhibiting many neurobiological effects including more complex dendritic arborization and enhanced recovery of function. Recently, our laboratory considered the nature of stimuli presented in enriched environments; specifically, we are interested in determining if rats housed in environments with natural objects (e.g., rocks, sticks) respond differently than rats housed in environments with artificial stimuli (e.g., plastic toys). Prior to these studies, pioneering naturalist Beatrix Potter commented that wild-caught mice were more intelligent than "fancy" rodents acquired from breeders, suggesting that natural environments may be more beneficial to mammals. To systematically investigate the influence of natural stimuli, rats were placed in environments with either artificial or natural stimuli that were matched according to function. Although cognitive abilities were not affected, higher DHEA/CORT ratios (associated with emotional resilience) and increased GFAP-ir in the hippocampus were observed in the natural enriched animals; further, this group also exhibited higher levels of diving in a forced swim task. A second study revealed that, after being exposed to a swim escape test, the natural enriched animals responded with less fos-ir in the amygdala and more fos-ir in the nucleus accumbens core. Spontaneous behavior during the dark phase was recorded for animals in each group; preliminary data indicate that rats in the natural enriched group interacted with items in their environment more than the artificial enriched condition. In related field work, wild raccoons that forage naturally also had higher DHEA/CORT ratios than raccoons living in a park and

eating human refuse out of garbage receptacles. These findings corroborate additional findings indicating that the artificial conditions of the laboratory may lead to distorted responses that aren't observed in an animal's conspecifics living in more natural conditions. As an increasing numbers of humans are moving to urban environments, consideration of the nature and origin of environmental stimuli is important for the maintenance of emotional resilience.

How does the urban environment get under the skin? Examples from urban mental health. Sandro Galea, MD, DrPH, Columbia University Mailman School of Public Health. Urban living has become the modal form of living for the majority of the world's population. Urban environments shape how we feel, think, and behave. Abundant studies have shown that different features of the urban environment are associated with behavioral health, including common mood-anxiety disorders and substance use. But, how do urban environments get 'under the skin'? How does exposure to the urban physical, social, and service environment influence behavior or the phenotypic manifestation of disorder. This presentation will draw on examples from a series of studies in urban areas, centrally New York City and Detroit to discuss the molecular and behavioral mechanisms that might explain how the urban environment influences behavior and brain disorders. We will draw on epigenetic, and gxE work that has the potential to both answer some of these questions and point to areas for future research.

Effects of Light Pollution on Neuroinflammation and Mood. Randy J. Nelson, Department of Neuroscience, The Ohio State University Wexner Medical Center, Columbus, OH 43017 USA. Humans and other organisms have adapted to consistent and predictable 24-h solar cycles, a stable temporal niche, but over the past ~130 years the widespread adoption of electric lights has dramatically transformed our environment. Instead of aligning behavioral and physiological processes to the natural solar cycle, individuals respond to artificial light cycles created by social and work schedules. Urban light pollution, night shift work, transmeridian travel, televisions and computers have dramatically altered the timing of light used to entrain biological rhythms. In humans and other mammals, light is detected by the retina and intrinsically photosensitive retinal ganglion cells project this information both to the circadian system and limbic brain regions. Therefore, it is possible that exposure to light at night, which has become pervasive, may disrupt both circadian timing and mood. Notably, the rate of major depression has increased in recent decades, in parallel with increasing exposure to light at night. Strong evidence already links circadian disruption to major depression and other mood disorders. Emerging evidence from the past few years suggests that exposure to light at night also negatively influences mood. This presentation will provide evidence from recent human and rodent studies supporting the novel hypothesis that nighttime exposure to light disrupts circadian organization, blunts the amplitude of circadian clock gene expression, provokes neuroinflammation, and contributes to depressed mood. I will address the complicated web of potential behavioral and physiological consequences resulting from exposure to light at night, as well as the large-scale medical and ecological implications that may result.

Violence and the City: Biomarkers in Children and Adults. Jovanovic, T. Emory University; Ressler, K. Emory University. Posttraumatic stress disorder (PTSD) occurs in some people after exposure to events that cause extreme fear or helplessness. High rates of trauma exposure and PTSD in low-income, urban populations underscore the urgent need for research in such samples. A growing number of studies indicate that low income individuals living in urban environments are at especially high risk for both exposure to violence and PTSD. In such samples, exposure to trauma may begin early in life; studies of children and young adults from similar samples suggest that initial trauma exposure during childhood or adolescence is common. Our research focuses on risk and resilience biomarkers of PTSD in adults and children from inner-city Atlanta. In this population, more than 80% of all individuals have been exposed to violence, including childhood abuse, assault, and domestic violence. However, only half of those have PTSD. The differential risk influencing who will develop PTSD is associated with multiple factors: it is in part genetic, with approximately a 30-40% heritability in risk for PTSD following trauma, and it depends on the individual's history, including adult and childhood trauma

and psychological factors which may differentially mediate fear and anxiety regulation. Therefore, PTSD is among the most likely of psychiatric disorders to be understood from the perspective of environmental influences interacting with genetic vulnerability, since diagnosis requires a specific, highly traumatizing, fear-evoking experience. In addition, a large amount of evidence now supports a model in which PTSD can be viewed, in part, as a disorder of fear dysregulation. Evidence suggests that a hallmark of PTSD neurobiology is exaggerated limbic system activity during fearful stimulation coupled with reduced top-down control of these brain regions by the prefrontal cortex. The presentation will describe our research on brain-based biomarkers, such as startle responses and neuroimaging data that have been associated with fear responses in PTSD. In addition, genetic and hormonal data demonstrating biological contributions to the disorder will be shown. Finally, intergenerational studies of mothers with PTSD will indicate biological and environmental risk factors for the disorders in children. Identification of vulnerable individuals allows for early intervention treatments, and investigating neural substrates of the disorder can provide for targeted brain-based treatment approaches.

10:30-11:30 **Keynote Speaker.** Cross-species translational studies of bipolar disorder. M. Geyer

Cross-species translational studies of bipolar disorder. Geyer, M. UCSD; Young, J. UCSD; van Enkhuizen, J. UCSD. Mania is the cardinal feature of Bipolar Disorder (BD) and is traditionally assessed using self- and observer-rating scales. These scales have limited the development and assessment of preclinical models of BD however, since they are not applicable to animals. In the new DSM-V classification of BD, an increase in energy or activity is required for the diagnosis of mania or hypomania. In order to overcome the reliance on verbal reports, a human Behavioral Pattern Monitor (hBPM) was developed recently as a reverse-translational approach to assess exploratory activity quantitatively. The hBPM was modeled after the well-established rodent BPM, which provides a multivariate assessment of the amount, structure, and sequences of exploratory motor behavior. In the hBPM, BD patients tested during acute episodes of mania exhibit a specific phenotype that differs from other clinical groups and is characterized by increased distance-covering activity, increased specific exploration, and perseverative spatial patterns of movement. This exaggerated exploratory activity appears to be at least partially due to trait characteristics, since euthymic BD patients show similar phenotypes, albeit to a reduced degree. Parallel animal experiments have shown that disrupting dopaminergic homeostasis by reducing dopamine transporter (DAT) function through either pharmacological or genetic manipulations produces a BD mania-like phenotype in mice as assessed by the mouse BPM. In related studies, both manic BD patients and mice having reduced DAT function were found to exhibit deficits in the prepulse inhibition of startle and increased risky behavior in cross-species versions of the Iowa Gambling Task. Such findings support the use of cross-species translational paradigms to investigate mania in humans and in rodent models of BD. These findings are consistent with the idea that impaired dopaminergic homeostasis due to chronic DAT inhibition may contribute to the pathophysiology of BD mania.

3:30-5:30 **Symposia: That's why they call it gambling: Neural mechanisms regulating risk/reward decision making.** Chair: Stan B. Floresco

What's better for me: Neural circuits mediating subjective decision biases. Floresco SB, University of British Columbia. Choosing between smaller, assured rewards or larger, uncertain ones requires reconciliation of competing biases towards more certain or riskier options. These conflicting urges reflect an interplay between distributed neural circuits linking the frontal lobes to subcortical regions processing emotional and reward-related information that in turn influence response selection. Each of these regions is interconnected with the dopamine system. Our studies have used a probabilistic discounting task to probe the interactions between these systems in regulating risk/reward decision making. Data will be reviewed showing that subcortical circuitry linking the amygdala and the ventral striatum appears to promote a more visceral bias towards larger, uncertain rewards, whereas prefrontal regions serve to temper these urges when riskier options become less profitable via top-down control over the amygdala. Dopamine D1 and D2 transmission within these regions also makes dissociable, yet complementary, contributions to risk/reward judgments, promoting either exploitation of current favorable circumstances or exploration of more profitable ones when conditions change. Dynamic fluctuations in tonic dopamine transmission in the prefrontal cortex and nucleus accumbens appear to encode distinct types of information related to decision making related to changes in reward availability, uncertainty and choice biases. On the other hand, phasic increases and decreases in dopamine activity, regulated in part by the lateral habenula, appear to play a key role in providing short-term information about recent outcomes that can bias subsequent choice behavior. These findings provide insight into the dynamic competition between these cortical/subcortical circuits that shape our decision biases and underlie conflicting urges when evaluating options that vary in terms of potential risks and rewards.

No pain no gain: dopaminergic modulation of risky decision making. Setlow, B. Depts. of Psychiatry, Neuroscience, & Psychology, University of Florida. Elevated risk taking (preference for large rewards despite the potential for adverse consequences) is associated with several neuropsychiatric disorders including addiction. To model risky decision making in animals, we have developed a behavioral task in which rats make discrete choices between a small "safe" food reward and a large, "risky" food reward which is associated with varying risks of mild footshock punishment. Rats in this task are sensitive to the risk of punishment, choosing the large reward when risk of punishment is low, and switching to the small, safe reward as risk of punishment increases. Importantly, there is considerable and stable variability among individual rats' performance in this task, such that they can be reliably classified according to their degree of preference for the large, risky reward. Prior work showed that this variability in risk taking predicts cocaine self-administration, supporting the validity of the task for modeling human behavior. To assess the role of dopamine signaling in risky decision making, we used a combination of behavioral pharmacological and gene expression approaches. Acute systemic administration of either amphetamine or the D2 dopamine receptor agonist bromocriptine reduced risk taking, whereas the D1 receptor agonist SKF81297 had no effect. Consistent with these data, the effects of amphetamine were attenuated by co-administration of a D2, but not a D1 antagonist. To assess relationships between individual differences in risky decision making and dopamine receptor expression, in situ hybridization was used to evaluate regionally-specific mRNA expression. Greater risk taking was associated with lower expression of D2 mRNA in both dorsal and ventral striatum. To assess the functional significance of these associations, the effects on risky decision making of acute intra-striatal administration of the D2 agonist quinpirole were evaluated. Quinpirole microinjection into ventral, but not dorsal striatum reduced risk taking, supporting the functional significance of the individual variation in D2 mRNA expression in this region. Finally, recent data show that lesions of the basolateral amygdala (which projects directly to ventral striatum, where it can modulate dopamine signaling) robustly increase risk taking. Together, these findings suggest that basolateral amygdala-ventral striatal dopamine (D2 receptor) signaling is critical for adaptive risky decision making.

You got to know when to hold 'em: prefrontal neural correlates of response inhibition. David Moorman; Department of Psychology, Neuroscience & Behavior Program; University of Massachusetts Amherst. Accurate decision-making requires the implementation of a number of sub-processes, regulated by diverse, overlapping, neural systems. Even basic decision-making tasks studied in the laboratory (for example Go/NoGo tasks) involve reward valuation and seeking, response planning, response execution, and response inhibition. More complex tasks (e.g., probabilistic or delay discounting or risky decision-making) involve even more extensive neural circuits. Here I will present recent results describing the prefrontal correlates of these fundamental components of decision-making. In a series of studies, we recorded the activity of neurons in medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC) of rats while they performed a simple discriminative-stimulus Go/NoGo task and then when the rewarded stimulus of the task was extinguished. These manipulations allowed us to investigate neural correlates of response execution (Go) and two forms of response-inhibition (NoGo, and extinction-based response inhibition). OFC neurons fired robustly prior to initiation of reward-seeking (Go), but not in relation to either non-rewarded stimuli (NoGo) or extinguished rewarded Go stimuli. In the mPFC, we compared activity in the dorsal prelimbic cortex (PL) to the ventral infralimbic cortex (IL), driven by the hypothesis that PL neurons would more strongly encode response execution and IL neurons would more strongly encode response inhibition. Instead, both PL and IL neurons encoded the initiation of the contextually-correct behavior: response execution when the Go stimulus was rewarded and response inhibition for either the NoGo stimulus or the extinguished Go stimulus. Thus across two frontal cortical areas – OFC and mPFC – we found neural representations of specific subcomponents of basic decision-making processes. Signals in the mPFC reflected the accurate recognition of context used to drive correct behavior (i.e., "knowing when to hold 'em") whereas signals in the OFC reflected the initiation of the reward-seeking response (i.e., "going all in"). These findings indicate that understanding the neural correlates of basic cognitive behaviors (e.g., response execution or inhibition) is essential for developing a comprehensive neuroscience of decision-making and is critical for characterizing disrupted systems in psychiatric diseases such as drug and alcohol addiction. Supported by PHS grants R21-DA032005, P50-DA015369, and R01-MH092868.

Good money after bad: Using mouse and human gambling tasks to explore why bipolar patients chase the risk. J. van Enkhuizen1,2, BL. Henry1, A. Minassian1, W. Perry1, M. Milienne-Petiot1,2, K. Higa1, MA. Geyer1,3, JW. Young1,3 1 Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804 2 Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584 CG Utrecht, The Netherlands 3 Research Service, VA San Diego Healthcare System, San Diego, CA. Background: Individuals with bipolar disorder (BD) exhibit deleterious decision-making, negatively impacting their lives. Commonly, these people make risky choices for rewards irrespective of the potential negative consequences. Such aberrant decision-making can be quantified using the Iowa Gambling Task (IGT), which requires choosing between advantageous and disadvantageous options based on different reward/punishment schedules. The mechanisms underlying this behavioral deficit are unknown, but may include the reduced dopamine transporter (DAT) functioning reported in BD patients. Using both human and mouse IGTs, we tested whether reduced DAT functioning would recreate the deficient decision-making of BD patients. Methods: We assessed the IGT performance of 16 BD and 17 healthy control (HC) subjects. We recorded standard IGT performance measures and novel post-reward and post-punishment decision-making strategies. Furthermore, we characterized a novel single-session mouse IGT using C57BL/6J mice (n=44). The BD and HC IGT performance were compared with the effects of chronic [genetic knockdown (KD; n=31) and wild-type (WT; n=28) mice] and acute [C57BL/6J mice (n=89) treated with the DAT inhibitor GBR12909] reductions of DAT functioning in mice performing this novel IGT. Results: BD patients exhibited impaired decision-making compared to HC subjects ($F(2,32)=3.5$, $p<0.05$). Both DAT KD ($F(2,36)=5.0$, $p<0.05$) and GBR12909-treated ($F(2,48)=32.1$, $p<0.001$) mice exhibited poor decision-making in the mouse IGT. The deficit of patients ($p=0.054$), KD, and GBR-treated mice ($p<0.05$) was driven by reward hypersensitivity. Conclusions: The single-session mouse IGT measures dynamic risk-based decision-making

similar to humans. Chronic and acute reductions of DAT functioning in mice impaired decision-making consistent with poor IGT performance of BD patients. Both patients and reduced DAT functioning mice had poorer decision-making driven by high reward-seeking irrespective of the risk. Hyperdopaminergia may therefore underlie the poor decision-making exhibited by BD mania patients.

3:30-5:30 Symposia: Behavioral endpoints in drug discovery: What does the Pharmaceutical industry need? Chair: Sophie Dix

Where Next? The Past, Present, and Future of Behavior in Drug Discovery. David McKinzie; Eli Lilly & Company. Since the beginning of the pharmacotherapeutic revolution in the mid-20th century, medicines for psychiatric disorders were often discovered serendipitously through astute clinical observations. For instance, the first successful antipsychotics, such as chlorpromazine, were originally developed as anti-histamines and anesthetic adjunctive agents, but were noted to have calming attributes that eventually led to their clinical use in psychotic patients. Iproniazid, one of the first anti-depressants, was originally evaluated as an agent to combat tuberculosis; although it proved to not be particularly effective in treating tuberculosis, patients reported robust elevations in mood which eventually led to clinical trials in patients with depressive disorders. Subsequently, animal behavioral pharmacology models of psychiatric disorders were developed by way of back-translational means, leading to scores of new medications based on similar pharmacology to the forerunner compounds. These animal models of psychosis or mood disorders have been used for decades to develop new compounds that shared considerable pharmacological overlap with clinically-used medications. However, as targeted mechanisms have diverged from established classes of medications (e.g., D2 antagonists for schizophrenia / 5-HT reuptake blockade for depression), the translation of preclinical efficacy into meaningful therapeutic clinical response remains poor. With the advent of new technologies within the fields of neuroimaging and genetics, tremendous advances have occurred in our understanding of the neuropathophysiology of psychiatric disorders. The use of behavioral paradigms in drug development flowschemes is increasingly complemented with the use of genetically-modified animals and concomitant physiological endpoints. Although not yet proven, it is hoped that these new scientific innovations will lead to greatly improved translational predictiveness for novel medications that better satisfy unmet clinical need. This talk will highlight the past, present, and future role of behavioral pharmacology in drug discovery.

Translatable assays for cognitive research: The use of touchscreens in drug discovery. Sophie Dix, *Senior Research Scientist, Eli Lilly & Co*. The high failure rate of Phase II and III clinical trials for treatments of psychiatric and neuro-degenerative disorders has brought into question the predictive validity of pre-clinical animal models and measures for neuroscience research. However the manner in which pre-clinical cognitive testing is performed bears little resemblance to the tests that are used in a clinical setting, while the reliance on questionnaires and rating scales makes the development of meaningful pre-clinical models difficult. Accordingly, a gap exists between the pre-clinical models which are used to create the rationale for a compound to advance to the clinic and the measures used to prove clinical efficacy. To bridge this "translational gap" it is necessary to use pre-clinical measures that have relevance to a clinical setting and also to use clinical measures that can be back-translated to the rodent. The use of touchscreen equipped operant boxes may present a unique opportunity to improve predictive validity of pre-clinical tests by facilitating the use of human-like experimental designs in the rodent, as well as rodent-like designs in the human. Moreover, the touchscreen approach allows the examination of cognitive processes that are not easily studied in a high-throughput fashion with existing methodologies like maze-based procedures or digging tasks. With the touchscreen approach, unlike most rodent cognitive test batteries, behavior is measured in the same testing system which allows trial design, stimuli, sensory modality and primary motivation to be held relatively constant. This makes it much easier to dissociate observed effects and to attribute them to changes in a domain or circuit specific manner, as opposed to when a wide variety of testing approaches are used. It is important to consider, however, that although many of the touchscreen paradigms show good translational face validity between humans and rodents, the way a

rodent performs a task and, hence the neural systems that are engaged, may differ between species. Appropriate validation of any touchscreen test battery is essential before the touchscreen approach can be use ability to model, understand, and treat the cognitive circuits that are disrupted in disease.

Combining *in vivo* electrophysiology and behavior – A circuit based approach to drug discovery. Liam Scott Pfizer Neuroscience Research Unit, USA. Preclinical research in the psychiatry field has been prolific over the last decade in identifying novel mechanisms which had efficacy in rodent behavioral models. Unfortunately the vast majority of these discoveries have not translated into clinical proof of concept. This poor success rate in predicting clinical efficacy has caused the field to reconsider its strategy for the characterization of new targets. One approach is to use electrophysiological techniques to investigate the neural circuit abnormalities in CNS disorders and the mechanisms of action of novel therapeutics in development. To do this we are developing a range of electrophysiological assays targeting specific phases of the drug discovery process. Firstly, as presented in this talk, we measure local field potentials from freely moving mice and assess target modulation in a translatable assay of sensory processing, showing how this type of measure can be used as a bridge between behavioral assays and clinical studies. Next, we use a delayed non-match to sample task on a T-maze whilst measuring the coherence of local field potentials in the hippocampus and prefrontal cortex in a genetically modified mouse model that shows impaired working memory. Lastly, we present data showing the activity of single hippocampal place cells recorded from freely moving mice in a U maze. The effect of pharmacological treatment on the encoding of the place fields of these neurons to a familiar environment as well as the remapping of these fields when the subject was placed in a novel environment will be presented. Overall we provide examples of how electrophysiological signals can be used to assess target modulation using a translatable endpoint, through to using purely preclinical techniques to refine our understanding of the mechanisms involved in modulating behavior in a symptom relevant task.

Imaging behavior: in vivo oxygen amperometry as a proxy for BOLD signal in rodents. (First Author) Gilmour G. (Affiliation); Eli Lilly & Co. Ltd. Functional magnetic resonance imaging (fMRI) techniques have been paradigm shifting with regard to the types of hypotheses that can be tested in cognitive neuroscience studies. These methodologies are finding their way into neuropsychiatric drug development programs, where they can potentially be used in several contexts, from "dose-finding" and patient stratification approaches to proof-of-concept trials. fMRI can be conducted in rodents, although limited at present to anaesthetized or restrained subjects, thereby confounding attempts to analyze behaviourally evoked signals. A translational gap exists where there is little a preclinical scientist can do to inform the design of a human imaging study. Together with a number of collaborators we have recently established an in vivo oxygen (O2) amperometry technique that allows measurement of neuronal activation in a manner homologous to human blood oxygen level-dependent (BOLD) fMRI. Up to four carbon paste electrodes can be implanted into the brain of a rat or mouse to measure in real time regional tissue O2 levels via constant potential amperometry. Recordings can be made in awake animals for periods of more than six months, either spontaneously behaving or performing maze or operant box based tasks. The presentation will firstly highlight the basic principles of in vivo O2 amperometry and demonstrate the close similarities of the amperometric O2 signal to the BOLD signal. Several preclinical applications of the technique will be discussed, from simple pharmacodynamic signals measured following administration of compounds to event related signals measured during appetitive learning tasks involving incentive delay, reversal and extinction. A very recent novel application will also be discussed involving assessment of functional connectivity between brain regions via correlations in ultra-low frequency O2 signal oscillation. This approach is currently being investigated for its potential to identify functionally connected "resting state" and task-engaged networks in behaving animals. To close, the presentation will discuss the values of the in vivo O2 amperometry technique in the context of neuropsychiatric drug discovery, which as well as simply allowing an imaging methodology to be applied much earlier in the discovery process also allows more detailed questions relating to construct validity of pharmacologically induced changes in behaviour to be conducted in awake rodents for the first time.

5:30-7:30 **Poster Session 1**

1. **Effects of Methamphetamine and Barren Housing on Allocentric Learning and Memory in Adult Rats.** Gutierrez, A. Division of Neurology, Cincinnati Children's Research Foundation, College of Medicine, University of Cincinnati; Amos-Kroohs, R.M. Division of Neurology, Cincinnati Children's Research Foundation, College of Medicine, University of Cincinnati; Williams, M.T. Division of Neurology, Cincinnati Children's Research Foundation, Department of Pediatrics, College of Medicine, University of Cincinnati; Vorhees, C.V. Division of Neurology, Cincinnati Children's Research Foundation, Department of Pediatrics, College of Medicine, University of Cincinnati. Chronic stress negatively impacts learning and memory (L&M). L&M can be improved by moderate stress. Cages with no bedding (barren; BAR) produce an increased glucocorticoid response in rats. Binge methamphetamine (MA) administration negatively affects certain types of L&M, although allocentric L&M as tested in the Morris Water Maze (MWM) has provided ambiguous results. The present study assessed the effect of BAR housing and MA administration on allocentric L&M. A 244 cm diameter MWM was used with the presumption this increases the sensitivity of the test. Adult Sprague-Dawley rats were housed in standard or BAR cages (clean cage and clean paper towel provided daily) for 3 weeks at which time animals were treated with 10 mg/kg MA 4x at 2 h intervals or saline. Two weeks post MA treatment, rats were tested in a 244 cm straight water channel to acclimate them to swimming, assess swim speed, and provide contingent reinforcement for finding the escape (hidden platform). Next animals went through 3 hidden platform phases (acquisition, reversal, and shift) in the MWM, each phase consisting of 6 days with 4 trials/day with randomized start and fixed platform positions. In each phase, hidden platform size was reduced progressively (10, 7, & 5 cm, respectively). On the 7th day of each phase, a single probe test was given with no platform. Finally, rats were tested on cued trials with the 10 cm platform with a visible cue mounted on it protruding above the water. This phase consisted of 2 days, 4 trials/day. A separate group of animals underwent the same housing and treatment with blood collected prior to drug treatment and 2 weeks after for plasma corticosterone determinations. Hippocampus, neostriatum, and nucleus accumbens were collected at the second blood collection time point. Monoamine levels in these regions will be examined by HPLC-ECD. Western Blotting will be performed to determine Glial Fibrillary Acidic Protein (GFAP) expression. L&M impairments were found on all 3 hidden platform phases in animals treated with MA with no changes in swim speed. Probe trials revealed deficiencies after reversal and shift phases, but not after acquisition. Irrespective of drug treatment, BAR animals performed slightly better than standard cage rats but only in acquisition. MA induces allocentric learning and reference memory impairments when tested in a large maze. BAR housing had a transient facilitatory effect on MWM performance but did not interact with MA treatment.

2. **Decreased myelin basic protein expression in the ventromedial prefrontal cortex of adult male rats enhances impulsive choice in a delayed discounting task.** S.M. Webb, M.A. McCloskey, D. Maliniak, M. Rangel, T. Alterman, C. Hudson, K.K. Szumlinski. Psychological and Brain Sciences, University of California at Santa Barbara, Santa Barbara, CA. Hypofunction of the prefrontal cortex (PFC) is consistently observed across many neuropsychiatric disorders. Research has primarily focused on the underlying neuronal pathology within the PFC impairing executive processes such as attention, behavioral inhibition, problem solving and decision-making. However, a disruption in neuronal support cells, such as oligodendrocytes and their associated myelin sheaths, may also contribute to these deficits. Myelin basic protein (MBP) is a major protein component within the myelin sheath and is necessary for the fusion of the intracellular leaflets. A deficit or excess of MBP leads to a loss of adhesion of the bilayers causing swelling of the cytoplasmic spaces, minimal spiral growth and fewer myelinated axons. Therefore, a disruption in the myelin sheath could alter neuronal transduction and manifest as hypofunction within a brain region. We hypothesized experimentally manipulating MBP by microinjection of a lentiviral vector (LVV) encoding a small hairpin RNA (shRNA) against MBP

transcripts within the ventromedial PFC (vmPFC) would impair a variety of PFC-dependent behaviors. Thirty-seven adult, male Sprague-Dawley rats were implanted with bilateral guide cannulae and microinjected intra-vmPFC with one of two different shRNAs against MBP or a control LVV. Three weeks post-infusion, animals were subjected to a behavioral test battery. Neither shRNA impaired memory processes assessed by the novel or displaced object recognition, or alternating T-maze tests, nor did they affect anxiety measured by behavior in the marble burying, light/dark box, or novel object tests. The shRNAs also did not influence sensorimotor processing/gating in pre-pulse inhibition of acoustic startle. However, MBP knock-down did elevate impulsive choice in a delayed-discounting paradigm. To the best of our knowledge, these data are the first to indicate that disruption of an oligodrocyte-specific MBP within the vmPFC impacts behavior, more specifically impulsive choice. Given the important role for MBP in myelin integrity, these data highlight the importance of further research on nonneuronal cellular targets as contributing to hypofrontality of relevance to the etiology of a number of neuropsychiatric conditions characterized by abnormal volitional control over behavior, including addictions, obsessive-compulsive disorder, attention-deficit hyperactivity disorder, psychotic and affective disorders. Supported by NIDA grant DA024038 to KKS

3. **Lesions of anterior and posterior subregions of the pedunculopontine tegmentum differentially affect sensorimotor gating.** Susanne Schmid, Jordan Robinson. Anatomy & Cell Biology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada. The pedunculopontine tegmentum (PPT) is part of the mesopontine cholinergic system with distinct anterior and posterior subdivisions. With fast sensory input and descending connections to brainstem locomotor centers, we predict posterior PPT (pPPT) mediates prepulse inhibition of acoustic startle reflex, a form of sensorimotor gating that affects attentional processes. Similar to pPPT cholinergic projections to ventral tegmental area, we predict anterior PPT cholinergic input to substantia nigra regulates dopamine release in striatum, which is important for reinforcement learning. We lesioned the anterior or posterior PPN in 350-400g male Sprague-Dawley rats with ibotenic acid (400nl with 0.062M). The extent of posterior cholinergic cell loss was significantly correlated with lower prepulse inhibition scores, consistent with our predictions for pPPT mediation of PPI. Anterior cholinergic cell loss was not correlated with performance in cued version of Morris water maze task, though lesions were likely insufficient. These results contribute to investigation of anterior vs. posterior PPT contribution to cognitive function.

4. **Selective agonism of α3, but not α1 subunit-containing GABAA receptors in the amygdala induces anxiolytic-like effects as measured by elevated plus maze in mice.** Gao, Y. University of Tennessee Health Science Center; Heldt, S. University of Tennessee Health Science Center. In recent years, pharmacogenetics studies reveal that α2-containing GABAA receptors (GABAARs) are necessary for the anxiolytic effect of benzodiazepines, while contradictory evidence shows that selective agonism of α3-containing GABAARs alone produces an anxiolytic effect. At present, vast majority of the studies using subtype-selective agonist/antagonist of GABAARs were carried out by systemic injections, thus the effects of the drugs are produced globally in the brain. In this study, we locally delivered subtype-selective agonists of GABAARs in basal-lateral amygdala (BLA, a key brain region that mediates anxiety-like behaviors), in hope to elucidate the specific roles of α1 and α3-containing GABAARs in this particular brain region. Zolpidem (a selective α1-containing GABAAR agonist, 0.5mg/mL), TP003 (a selective α3-containing GABAAR agonist, 0.5mg/mL), or vehicle were administered via micro-infusion to the BLA of C57/BL6J mice and the subjects were tested 5 min later on the elevated plus maze. We found that zolpidem, at 0.5mg/mL dose, did not alter the percentage of time spent and the distance traveled in the open arm. TP003, on the other hand, significantly increased both measures. No significant differences in total crossing and distance traveled in the closed arm were observed. These results indicated that selective agonism of α3- but not α1-subunit-containing GABAARs in the BLA

produced an anxiolytic-like profile at doses studied. We infer that although the differential distribution pattern of α subunits among different brain regions might contribute to the selective outcome of systemic injection of selective agonist, it is also evident that within BLA, different α subunits exert different functions in regulating anxiety-like behaviors. We are currently investigating the effect of zolpidem and TP003 at a range of doses to better understand the pharmacological effects of zolpidem and TP003 in the BLA.

5. **Anabolic steroids modulate fatty acid abundance and metabolism in the hippocampus of adolescent rats.** 1Santigo-Gascot ME, 2Chorna NE, 1Barreto-Estrada JL. 1Department of Anatomy and Neurobiology, Medical Sciences Campus, University of Puerto Rico, San Juan, PR 00936 2Department of Biology, Metabolomics Research Center, Río Piedras Campus, University of Puerto Rico, Río Piedras, PR 00935. The misuse of anabolic androgenic steroids (AAS) in adolescents and young adults has become a major public health problem. Previously, we found that a single or chronic dose of the AAS, 17-methyltestosterone (17-meT, 7.5 mg/kg), produced a significant impairment of inhibitory avoidance learning in periadolescent male rats. Since recent studies showed that modulation of the FA profile accounts for exercise-induced enhancement of spatial learning, we searched for AAS-modulation of FA in the brain. For this purpose, we trained periadolescent rats in the inhibitory avoidance task while treated with 17-meT. Thereafter, the FA profile was determined in the hippocampus, cerebral cortex and cerebellum. Among the FA found in the lipidomics profile are: palmitic, stearic, oleic, linoleic and docosahexaenoic acid (DHA). Also, we found that 17-meT induced a strong pattern of FA separation in the hippocampus as measured by principal component analysis (PCA). PC loadings showed that palmitc and stearic acids positively contributed to this AAS-induced separation. Regarding metabolism, we found that steroid treatment significantly affects oxidative processes. Our results suggest that FA synthesis and metabolism might be important targets for AAS-induced modulation of learning and memory. This project was supported in part by grants from NIH-NCRR (5P20RR016470) and NIH-NIGMS (8P20GM103475).

6. **Exposure to NMDA Receptor Antagonists at P7 Alters Prepulse Inhibition at P21 in Rats.** Janace J. Gifford*, Rachel A. Zacharias*, Shinchung Kang, Christopher P. Turner, Brian L. Thomas. Baldwin Wallace University Department of Psychology and Neuroscience Progam. *These authors contributed equally. Evidence suggests that anesthetic compounds can impair normal brain development and impair auditory processing during infancy (Wilder et al., 2009). In the present study, neonatal rats were exposed to the anesthetic drugs MK801 (1 mg/kg; n = 13) or ketamine (20 mg/kg; n = 15) at P7 and were then compared with saline control animals (n = 13) once per week from P8 to P70 on a prepulse inhibition (PPI) task. At P21, results indicated that ketamine decreased peak and average startle amplitude (over trials) on low and high prepulse and pulse only trials. MK801 similarly decreased the startle response, but to a lesser degree than ketamine. Ketamine and MK801 have been used in rodent models of schizophrenia because hypo-function of NMDA receptors has been shown to contribute to the etiology of the disease (Harris et al., 2003). Persons with schizophrenia have difficulty filtering sensory input, which can be revealed through the PPI task (Harris et al., 2003). Thus, neonatal exposure to NMDA receptor antagonists can cause deficits in prepulse inhibition, a symptom commonly observed in persons with schizophrenia and/or Alzheimer's disease (Swerdlow et al., 2008).

7. **Repeated amphetamine exposure induces behavioral, neurophysiological and molecular alterations of dopaminergic function in the basolateral amygdala.** Dept of Psychology, Brain Research Centre, University of British Columbia. Chronic abuse of amphetamine (AMPH) impairs cognitive processes associated with the limbic system. Rodent studies showed that repeated psychostimulant exposure causes behavioral, neurochemical and neurophysiological changes in modulatory effects of the mesolimbic dopamine (DA) on various regions of the limbic circuits (e.g.,

prefrontal cortex, nucleus accumbens). However, relatively few studies investigated physiological changes in the basolateral amygdala (BLA). We therefore investigated how repeated AMPH (2mg/kg i.p. every 48hr, followed by at least two-week wash out) may alter behavioral, neurophysiological and molecular properties of the BLA. We observed that repeated AMPH did not affect Pavlovian approach learning for sucrose pellets, but impaired acquisition of a novel instrumental response for conditioned reinforcement, a classic test of BLA function. In a separate cohort of rats, we performed in vivo single-unit recording from BLA neurons in acute urethane-anesthetized rats. BLA neurons showed increased sensitivity to the inhibitory effects of phasic DA release in rats exposed to repeated AMPH. Burst stimulation of DA neurons caused a pronounced and reliable suppression of neuronal firing in the BLA relative to saline-treated rats. This DA hypersensitivity appeared to be dependent on increased D2 receptors sensitivity. Specifically, we observed that in the controls, 0.2 mg/kg dose (i.v.) of the D2 agonist qunipirole suppressed spontaneous firing of BLA neurons. In comparison, repeated AMPH treatment shifted the dose-response curved to the left, wherein lower doses of quinpirole (0.02-0.04 mg/kg) were effective in suppressing BLA neuron firing. In keeping with these findings, a subsequent western blot analysis revealed that repeated AMPH treatment tended to increase D2 receptor protein expression in the BLA relative to saline controls. Lastly, we observed that direct intra-BLA infusion of quinpirole in drug-naïve rats disrupted responding for conditioned reinforcement in a similar manner to repeated AMPH treatment. Collectively, we provided behavioral, physiological, and molecular evidence suggesting repeated AMPH increases D2 receptor expression in the BLA, causing an increased inhibitory tone within the BLA. These findings suggest impairments in reward-related functions observed in stimulant abusers, particularly those related to stimuli associated with natural rewards, may be due to dopamine D2 hyperactivity within the BLA.

8. **Effects of Adolescent Nicotine Exposure on Spatial Learning and Memory in the Adult Male Rat.** Michelle Blose, B.A. Introduction: Recent studies have discovered that nicotine exposure in rats during adolescence produces an increase in apoptotic cell death in hippocampal regions and significant deficits in adult serial pattern learning. Method: Eleven male Long-Evans rats were injected intraperitoneally for 30 days with either nicotine (N=5) or saline (N=6). The nicotine's dose was 1.0 mg/kg/day (expressed as a free-base). Following a two day delay, the adult rats' spatial learning was examined using the Morris water maze consisting of four trials per day for five days. A week following the conclusion of the acquisition phase trials, another four tests were conducted. Results: In the retention phase, there was a significant difference between the nicotine and the control group. A 2 (dose) X 4 (trial) X 2 (day) Repeated Measures ANOVA revealed significant main effects during spatial retention for day of the experiment, $F(1,9)= 137.14$, $p<0.001$, trial, $F(3,27)=27.427$, $p<0.001$. Also, there was a significant drug main effect between-subjects, $F(1,9)=28.563$, $p<0.001$. The test revealed a significant day x drug interaction, $F(1,9)=21.934$, $p=0.001$ as well as a trial x drug interaction, $F(3,27)=4.147$, $p=0.015$. In addition, it revealed a significant day x trial interaction, $F(3,27)=19.442$, $p<0.001$. Lastly, the ANOVA confirmed a day x trial x drug interaction, $F(3,27)=3.051$, $p=0.046$. Also, a 2-tailed equal variance t-test was conducted for control rats comparing day 1 versus day 5 and $p<0.001$ and for experimental rats, comparing day 1 versus day 5, $p<0.001$. A t-test was run on control rats comparing day 5 versus day 12, $p<0.001$ and for experimental rats, comparing day 5 versus day 12, $p<0.001$. Therefore, day 1 versus day 5 shows there was learning in both groups. Day 5 versus day 12 shows that there was no retention. A t-test was run comparing day 12 experimental rats and day 12 control rats, $p<0.05$. There was a significant difference between control and experimental rats on day 12. Conclusion: Based on results, it is clear that the adult rats' spatial learning and memory were affected in the retention phase. Both groups performed worse on day 12 compared to the last day of acquisition (day 5); however, the nicotine caused a greater impairment in retention. The nicotine did affect spatial learning and memory on day 12. These results show that nicotine has the ability to cause deficits in learning and memory.

9. **Cyclo-Glycyl-glutamine Blockade of the Alcohol Deprivation Effect in P Rats.** Garth E Resch, Jennifer Lindgren, and C. Wayne Simpson at SBS and UMKC School of Medicine. The repeated alcohol deprivation effect (ADE) has been proffered as a model of human alcoholism, resulting in elevated consumption after a deprivation, increased baseline drinking over time and, at some point, loss of control over drinking. The dipeptide cyclo-glycyl-glutamine (cGQ) reduces ongoing ethanol consumption but has not previously been tested for blockade of ADE and is the subject of this report. Male P rats were first stabilized on alcohol then placed on a repeated ADE paradigm of 9 days deprivation and 14 days reinstatement. The cycle was repeated for 33 weeks. Voluntary 24 h ethanol intake was recorded for saline treated control and cGQ treated groups. The data for serial ADE show cGQ blocks ADE 1) early in the series of repeated deprivations, 2) late in the series, after a number of deprivations, and 3) after loss of control. Additionally, cGQ may suppress the rise in baseline drinking compared to saline vehicle controls. Finally, cGQ shows no apparent side effects or toxicity. The data support the conclusion that cGQ blocks ADE and suggests the dipeptide may effect long term changes in neural adaptation with repeated exposures to the dipeptide.

10. **Reactivation of cocaine reward memory engages the Akt/GSK3/mTOR signaling pathway.** Shi, X.Department of Pharmacology & Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA 19140; Unterwald, EM. Department of Pharmacology & Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA 19140. Reconsolidation of cocaine reward memory can be attenuated by inhibition of glycogen synthase kinase-3 (GSK3). In this study, GSK3 and its major upstream (Akt) and downstream signaling molecules (β-catenin, mTORC1) were measured in specific brain areas to determine whether the Akt/GSK3/mTOR and/or Wnt/GSK3/□-catenin signaling pathway is involved in cocaine-associated memories. Adult male CD-1 mice underwent cocaine conditioned place preference for 8 days. Twenty-four hours after the test for place preference on day 9, half of the mice were confined to the previous cocaine-paired compartment in a drug-free state for 10 minutes to reactivate cocaine-associated memories and were euthanized immediately at the end of the cue exposure. The other half were kept in their home cage and served as a no-reactivation control. Western blotting indicated that levels of phosporylated AktThr308, GSK3αSer21, GSK3βSer9, mTORC1, p70SK6, but not β-catenin, were down-regulated ($p<0.05$) in the nucleus accumbens and hippocampus after reactivation of cocaine cue memories. Levels of pAkt and pGSK3α/β were also reduced in the prefrontal cortex ($p<0.05$). Since reduced phosphorylation of GSK3 indicates heightened enzyme activity during memory retrieval, and since GSK3β is part of a multi-protein NMDA receptor complex, the role of NMDA receptors in the reconsolidation of cocaine-related memory was studied. Administration of NMDA receptor antagonist MK-801 (0.3mg/kg) immediately after the 10 min exposure to cocaine-paired chamber disrupted the previously established place preference ($p<0.05$). These findings suggest that the Akt/GSK3/mTORC1 pathway is critically involved in the reconsolidation of cocaine contextual reward memory. The blockade of NMDA receptors, similar to inhibition of GSK3β □ can prevent the reconsolidation of cocaine reward memories, which makes NMDA receptor a potential therapeutic target in treatment of cocaine addiction.

11. **Sociosexual behaviors of male rats (Rattus norvegicus) in a seminatural environment.** Chu, X. Department of Psychology, University of Tromsø; Ågmo, A. Department of Psychology, University of Tromsø. In the wild, male rats copulate in groups consisting of several males and several sexually receptive females. This is quite different from the traditional one-male – one female pair used in the laboratory. The few published studies of sexual behavior in groups of rats report very limited data based on short periods of observation. To describe male sociosexual behaviors more precisely in an ecologically valid procedure, groups of rats (3 males and 4 cycling females) were housed in a seminatural environment consisting of a burrow and a large open area. Sociosexual interactions were recorded for the entire period of behavioral estrus for each female. The results showed that the

traditional way of conceiving male sexual behavior as a series of ejaculations in which the last ejaculation is followed by a long period of sexual inactivity turned out to be inadequate. Instead, male sociosexual behaviors occurred in bouts (the period from the initial mount until the beginning of a period (> 60 min) of sexual inactivity) which could be ended either by mount (39 ± 6 %), intromission (21 ± 7 %), or ejaculation (40 ± 8 %). The males performed a mean ± SEM of 132 ± 32 mounts, 53 ± 5 intromissions, 6 ± 0.5 ejaculations and 4.2 ± 0.5 copulatory bouts during the 8 days experiment. Copulatory bouts had mean duration of 2.8 ± 0.4 h. During a bout, 77 ± 1 % of the time was spent resting and grooming whereas 8 ± 1 % of the time was used pursuing the receptive female. The copulatory acts themselves took a very small fraction of the time (less than 0.2 %). Within a bout, the intensity of sexual behavior remained quite stable. Interestingly, there was no decline as the end of the bout approached. The interbout interval was 101 ± 11 min. There was no relationship between the last event in the preceding bout and the interbout interval. Regardless of whether there was single or multiple females in estrus, the males copulated with all available females in an apparently random way. When more than one female was in estrus, the males switched partner more frequently after intromission or ejaculation than after mount. Nevertheless, it appears that male rats are completely promiscuous and change partner several times within a bout. Concerning the use of space, it was found that social behaviors like sniffing and anogenital sniffing were more frequent in the burrow whereas sexual interactions (copulatory acts and pursuit of the receptive female) were more frequent in the open area.

12. **Dose-dependent effects of amphetamine challenge on locomotion following chronic methamphetamine exposure in mice: divergent quantitative and qualitative effects of BDNF deficiency.** Manning, E. The Florey Institute of Neuroscience and Mental Health; Halberstadt, A. Univeristy of California, San Diego; van den Buuse, M. The Florey Institute of Neuroscience and Mental Health. Methamphetamine (METH) abuse is associated with increased risk of developing psychotic disorders that closely resemble schizophrenia. Altered brain-derived neurotrophic factor (BDNF) signalling has been implicated in both the pathophysiology of schizophrenia and the effects of METH in the brain. To model aspects of the positive symptoms of schizophrenia, a common behavioural paradigm is the measurement of locomotor hyperactivity following acute administration of psychostimulant drugs like amphetamine, which induce subcortical dopamine release similar to that which is thought to contribute to psychosis. However, simple measurements of hyperactivity may not adequately describe the effects of psychostimulant drugs on behaviour. The aim of the present study was therefore to use a qualitative behavioural analysis to assess the effects of chronic METH pre-treatment on an amphetamine challenge in BDNF heterozygous mice (HETs) and wild-type controls (WT). Starting in late adolescence, BDNF HETs and WTs were treated for three weeks with escalating doses of METH, ranging from 1mg/kg once daily to 4mg/kg twice daily. Following 2 weeks drug withdrawal, mice were injected with saline or increasing doses of amphetamine and locomotor behaviour was measured using photocell activity chambers (Med Associates). Both quantitative (distance moved) and qualitative (spatial D for geometric aspects and entropy for sequential aspects) analysis were performed. Amphetamine reduced spatial D and increased entropy in a dose-dependent manner, indicative of straighter locomotor paths and more random locomotor paths, respectively. METH pre-treatment enhanced the effect of 1mg/kg amphetamine to increase distance moved, reduce spatial D and increase entropy irrespective of genotype (dose x METH treatment $p<0.01$). In contrast, METH enhanced the locomotor hyperactivity elicited by 3mg/kg amphetamine in WT mice, but not BDNF HETs (METH treatment x genotype x dose x time block, $p=0.008$) and while it reduced the effect of amphetamine to increase entropy in BDNF HETs, it had no effect in WT mice (dose x METH treatment x genotype, $p=0.012$) or on spatial D changes. These studies demonstrate a significant divergence between quantitative and qualitative aspects of amphetamine-induced changes in locomotor behaviour in BDNF HETs following METH treatment. This finding supports the value of computational analysis of qualitative measures of locomotion when studying the effects of psychostimulant drugs.

13. **Preferential activation of immature neurons in the temporal dentate gyrus by cocaine place preference.** Jeffrey L. Barr * and Ellen M. Unterwald, Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA. Intense craving for drug and relapse are observed in addicts who are exposed to environmental stimuli associated with drug-taking behavior even after long periods of abstinence. The hippocampus is a brain region known to be involved in spatial processing, taking place preferentially in the septal hippocampus, and emotional processing, taking place predominantly in the temporal hippocampus. Conditioned place preference (CPP) is an animal model of context-conditioned reward. The dentate gyrus is a hippocampal sub-region particularly important for the acquisition of cocaine-induced CPP and is a site of continuous neurogenesis which has been implicated in the vulnerability to develop drug taking behavior. Therefore, we aimed to explore the role of newly generated neurons in drug reward-context association by examining the activation, as determined by expression of the immediate early gene c-fos, of young and mature granule cells in the septal and temporal dentate gyrus of adult rats that were re-exposed to a drug-paired environment following the development of cocaine place preference. The overall level of c-fos expression was increased in both the septal and temporal dentate gyrus of animals that developed place preference and were re-exposed to the drug paired environment compared with re-exposure to a neutral environment. Overall level of neurogenesis, as detected by the S-phase marker 5'-bromo-2'-deoxyuridine (BrdU) and the immature neuron marker doublecortin (DCX), was greater in the septal dentate gyrus of all rats compared to the temporal dentate gyrus. However, activation of new neurons (DCX + c-fos) was greater in the temporal dentate gyrus of cocaine-conditioned rats re-exposed to the drug-paired environment compared to re-exposure to a neutral environment. Therefore, newly generated neurons, in the temporal dentate gyrus in particular, are involved in aspects of drug reward-context memory formation. Support: P30 DA13429 and T32 DA007237

14. **Neuropsychological functioning and Emotional disturbance: A comparison amongst Mentally Retarded and ADHD children.** Dr. Amra Ahsan. Neuropsychology offers an excellent theoretical framework to work in the assessment of a heterogeneous population such as individuals with Mental retardation (MR) and Attention deficit hyperactivity disorder (ADHD). The present study attempts to investigate the Neuropsychological functioning and extent of Emotional disturbance exhibited by MR, ADHD and normal children. It also tries to see how these three groups perform in relation to emotional disturbance. For this a comparative study was done. The sample of 180 children in the age range of 5 to 14 years was taken. Of these, 60 children were mentally retarded, 60 children were ADHD and 60 were normal children. The sample of MR and ADHD children included in the present study were diagnosed according to DSM-IV-TR Criteria. Cognistat (Gupta, & Natasha, 2009) was administered on these 180 children individually to assess their neuropsychological functioning. For administering the Emotional disturbance scale (Epstein & Cullinan, 1998), the investigator contacted the teachers/caregivers personally and requested them to give their response on each statement in relation to the children's emotional competence. The data, thus, obtained were tabulated group wise and were statistically analyzed to draw necessary inferences. The results show that MR and ADHD children performed poorly on various aspects of neuropsychological functioning as compared to normal children. Further, it was found that ADHD children had secured lower scores on most of the dimensions of neuropsychological functioning, while MR children had performed poorly only on few dimensions (in comparison to ADHD). Across the three groups, ADHD children were more emotionally disturbed followed by MR children and normals, and high emotionally disturbed MR and ADHD children scored low on the total score as well as on different dimensions of neuropsychological functioning.

15. **Interaction of diet and a misaligned circadian rhythm in an animal model of shift work.** Cyrilla H. Wideman and Helen M. Murphy - John Carroll University. Obesity in America has risen sharply in the

past three decades. Maintenance of the balance between diet and activity depends upon the body's naturally occurring circadian rhythm, a pattern of rest and activity. When this pattern is disrupted, as seen in people on shift work schedules, many systems cannot adjust and debilitating effects are seen in body weight, food intake, adipose tissue deposition, metabolism, and activity. Utilizing a rodent model, the present experiment sought to understand the effects of a high-fat diet and circadian de-synchronization on body weight, caloric intake, feed efficiency, adiposity, and activity. Twenty-four male Long-Evans rats were placed in cages containing a running wheel equipped with a monitor to record wheel revolutions. Two rooms were utilized with twelve rats in each room. During a seven-day habituation period, both rooms followed a 12-hour/12-hour light-dark cycle. An experimental period lasting three weeks followed. Room 1 contained twelve rats on a normal light/dark cycle. Six rats received a high-fat diet, and six rats received a control diet. Care and handling occurred at the onset of the dark cycle. Room 2 contained twelve rats on an altered light/dark cycle. Six rats received a high-fat diet, and six rats received a control diet. Care and handling occurred at the beginning of the light cycle. Rats fed a high-fat diet gained more body weight and had significantly more adiposity than those fed a control-diet, whether fed during the normal dark cycle or an altered cycle. Of particular interest were the findings that light-fed animals consumed significantly fewer calories than dark-fed animals and feed efficiency was significantly more positive in light-fed animals, suggesting that metabolic conditions were compromised under altered circadian conditions. There was also a dramatic decrease in activity levels in those animals with altered circadian rhythms. Results indicate that a high-fat diet and circadian misalignment lead to significant disruptive changes in the variables examined. These changes mimic those observed in humans working on shift work schedules.

16. **Exercise increases expression of neurotrophic factors in hippocampal microglia of aged mice.** Littlefield, A.; Setti, S.; Diaz, C.; Guendner, E.; Kohman, R.; Department of Psychology, University of North Carolina Wilmington, NC, 28403, USA. The brain's resident immune cells, microglia, can express various forms of activation including the classic inflammatory and the alternative neuroprotective phenotype. Aging causes microglia to become partially activated towards the inflammatory phenotype, resulting in chronic low-grade neuroinflammation that can lead to cognitive deficits. When in the alternative neuroprotective state; microglial cells can release neurotrophic factors including brain-derived neurotrophic-factor (BDNF) which is involved in neural development, synaptic plasticity and cell survival. Prior work has shown that exercise may be effective at shifting the primed microglia in aged animals towards the alternative phenotype. Exercise has been shown to elevate BDNF levels, but whether this effect occurs within microglia is unknown. The current study examined whether exercise would increase the proportion of BDNF positive microglia in the dentate gyrus of the hippocampus. In addition we assessed whether an acute immune challenge with the bacterial endotoxin lipopolysaccharide (LPS) would alter microglia expression of BDNF; and if exercise could protect against the effects of LPS. Adult and aged male C57BL/6J mice were individually housed with or without running wheels for a total of 9 weeks. Mice received a single LPS (250 µg/kg) or saline injection 5 weeks after beginning exercise or sedentary housing conditions. Tissue was collected 4 weeks after LPS or saline treatment. Immunofluorescence was conducted to measure co-expression of the neuroprotective indicator BDNF with the microglia marker Iba-1. Exercise increased the proportion of microglia expressing BDNF in aged mice. LPS caused a decrease in the proportion of BDNF positive microglial cells, even in the presence of exercise. Findings indicate that voluntary wheel running may promote a neuroprotective microglia phenotype in aged mice.

17. **Expression of mutant DISC1 in Purkinje cells affects Purkinje cells morphology and produces cognitive and social abnormalities in adult mice.** Alexey V. Shevelkin(1,4), Bagrat N. Abazyan(1), Berry Button(1), Gay L. Rudow(2), Christopher A Ross(1,3), Juan C. Troncoso(2), Mikhail V. Pletnikov(1,3). Departments of (1)Psychiatry and Behavioral Sciences, (2)Pathology, (3)Solomon H.

Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, (4)P.K.Anokhin Inst. Norm. Physiol, Moscow, Russian Federation. Disrupted-In-Schizophrenia-1(DISC1) and its variants have been associated with neurodevelopmental disorders, including schizophrenia and autism spectrum disorders (ASD). Purkinje cells (PC) express DISC1. We generated a mouse model of inducible and selective expression of mutant DISC1 in PC. Here, we sought to analyze the brain and behavioral alterations in this transgenic mouse model. We evaluated volume of the cerebellum and PC in mice at postnatal (P) day 21 and assessed behavioral phenotype in male and female mice of 3–7 months of age using a series of tests relevant to schizophrenia and ASD, including novelty-induced activity, elevated plus maze, Y maze, object and place recognition, fear conditioning and rotarod. We found a significant decrease in Purkinje cells size. Neither total number of PC nor volume of the cerebellum were significantly altered in mutant DISC1 mice. No cellular markers of inflammation were observed in mutant mice. Neurobehavioral phenotyping showed abnormal social interaction, hyperactivity in open field and deficient novel object recognition in male mice. We observed no group differences in elevated plus maze, spontaneous alteration or spatial recognition in Y maze. Our findings indicate that mutant DISC1 affects PC morphology and produces cognitive and social abnormalities in adult mice. This may have the potential to advance our knowledge of the role for DISC1 in maturation and function of the cerebellum related to neurodevelopmental disorders. Supported By: 1F05MH097457-01

18. **Ketamine prevents the development of avoidance behavior after social defeat stress in adolescent male mice.** Nieto, S. California State University San Bernardino; Riggs, L. California State University San Bernardino ; Dayrit, G. California State University San Bernardino; Flores, E. California State University San Bernardino; Cao, V. California State University San Bernardino; Shawhan, K. California State University San Bernardino; Cruz, B. California State University San Bernardino; & Iñiguez, S. California State University San Bernardino. Approximately 10% of children and adolescents are diagnosed with major depressive disorder (MDD). Currently, there are limited therapeutic agents to treat MDD in juvenile populations, when compared to the numerous options available for adults. To make matters worse, about 50% of adolescents with MDD are unresponsive to available treatments, which demonstrates the need to identify alternative pharmaceutical compounds for the management of juvenile MDD. In adult populations, ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has recently shown the capacity for rapid-acting and long-lasting antidepressant efficacy in both preclinical and clinical studies. Thus, to examine whether ketamine could be a potential rapid and effective therapeutic agent for juvenile MDD, we exposed adolescent male c57BL/6 mice (postnatal day [PD]35) to 10 days of social defeat stress – a common paradigm used to induce depression-like behaviors in rodents. Specifically, separate groups of defeated and non-defeated (control) adolescent mice were administered with saline or ketamine (20 mg/kg) either after each (chronic), or the last (acute) episode of defeat stress. Twenty-four hr later (PD45), all mice were tested for depression-like behavior, as inferred from the social interaction test (n=7-12 per group). As expected, adolescent defeated mice administered with saline (both chronic and acute) exhibited a depressive-like phenotype (i.e. increased social avoidance). Conversely, both chronic and acute exposure to ketamine prevented the development of the stress-induced avoidance phenotype seen after social defeat stress. Together, these findings indicate that the anesthetic ketamine may be a promising novel agent for the treatment of juvenile MDD.

19. **Effect of high fat diet consumption on endotoxin-induced cognitive deficits.** Setti, S., Littlefield, A., Diaz, C., Jones, A., Johnson, S., Kohman, R. A. University of North Carolina Wilmington. Diet-induced obesity (DIO) has been associated with impaired immune function. Activation of the immune system induces behavioral alterations, collectively known as sickness behavior, as well as cognitive deficits. Prior research has shown that DIO can exaggerate and prolong the behavioral response to an immune challenge (Pohl et al, 2013), but whether DIO enhances the learning deficits associated with

inflammation is unknown. The current study examined whether DIO would show greater cognitive deficits following an immune challenge with the endotoxin, lipopolysaccharide (LPS). Adult female C57BL/6J mice were free-fed either a high-fat diet (HFD; 60% fat) or a control diet (CD; 10% fat) for a total of 5 months. After 4 months, mice were systemically injected with either LPS or saline, and 4 hours later tested for spatial-learning in the Morris water maze (MWM). One month later, mice received the same treatment (i.e., LPS or saline) they received prior to the MWM task. Four hours after treatment, brain, adipose, and spleen samples were collected. Data collection is still in progress, but preliminary results indicate that DIO may diminish the LPS-induced cognitive deficits. To determine whether the behavioral alterations reflect a modified inflammatory response in the DIO mice, we will assess peripheral and neural production of proinflammatory cytokines. Currently, our data indicate that the cognitive impairment associated with inflammation interacts with an organism's diet.

20. **Therapeutic effects of methylene blue on cognitive impairments following chronic cerebral hypoperfusion.** Allison Auchter, Justin Williams, Bryan Barksdale, Francisco Gonzalez-Lima (all authors affiliated with the 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 animals 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 surgery, animals went through a battery of different behavioral tests, including an open field task, visual water maze task and odor-recognition task. Results reveal that rats that underwent 2-VO surgery show worse performance in the visual water task and odor-recognition test without showing differences in general motor activity or swimming ability. Additionally, daily administration of MB was able to prevent some of the cognitive deficits that resulted from cerebrovascular insufficiency. Specifically, after 10 days of training on three different elemental discrimination patterns in the visual water task, 2-VO animals showed lower performance in a memory probe test. However, animals that received daily injections of MB performed significantly better than saline-treated subjects. Similarly, in the odor-recognition task, 2-VO MB-treated but not 2-VO saline-treated animals preferentially investigated a novel odor over an odor that was explored the previous day, indicating improved memory for the familiar odor. These data suggest that MB treatment may be therapeutic in conditions of chronic cerebral hypoperfusion.

21. **DISC1 mutation and adolescent cannabis exposure interact to produce adult psychopathology.** B. Abazyan, S. Abazyan, C. Yang, A. Kamiya, and M. Pletnikov. Both genetic and environmental factors contribute to the development of major psychiatric disorders. Identification of expression of a psychiatric risk gene, Disrupted-In-Schizophrenia (DISC1), in astrocytes allows for evaluating the role of astrocytes in gene-environment interaction in mental illness. Adolescent cannabis exposure has been associated with the elevated risk for cognitive deficits in adulthood in vulnerable individuals. Recent studies have demonstrated that cognitive effects of tetrahydrocannabinol (THC), a major component of marihuana, are mediated by CB1 receptors on astrocytes. We sought to explore the cognitive effects of interaction between astrocytic mutant DISC1 and adolescent exposure to THC in mice. Control and mutant DISC1 male mice were chronically treated with vehicle or THC (8.0 mg/kg, sc over 20 days) starting at postnatal (P) day 32 (adolescent exposure) or at P70 (adult exposure). Three weeks after the last injection mice were studied in a battery of behavioral tests relevant to schizophrenia, including activity in open field, anxiety in elevated plus maze, spontaneous alteration and spatial recognition in Y maze, novel object recognition, novel place recognition test and fear conditioning. Compared to all other

groups, THC-treated DISC1 mice exhibited increased anxiety and poorer memory for novel object or place and impaired spatial recognition and conditioned fear memory. We did not find significant group differences in novelty induced hyperactivity or spontaneous alternation. If expression of mutant DISC1 was shut down with doxycycline during adolescent THC exposure, no significant effects of THC were found. We are now testing the effects of adult THC exposure in mice to evaluate time-dependency of interaction. These findings suggest that long-term cognitive impairment can result from adolescent interaction between astrocytic genetic risk factors and THC exposure. Our results can be relevant to the pathogenesis of schizophrenia and related mental disorders.

22. **Chronic leptin antagonist administration to the VTA increases food intake without altering motivation to obtain either high fat or high sugar pellets: dissociation between "liking" and "wanting".** Scarpace, PJ. Department of Pharmacology and Therapeutics, University of Florida; Matheny, M. Department of Pharmacology and Therapeutics, University of Florida; Khamiss, DC. Department of Psychiatry, University of Florida; Nwokolo, JA. Department of Psychiatry, University of Florida; Toklu, HZ. Department of Pharmacology and Therapeutics, University of Florida; Tümer, N. Department of Pharmacology and Therapeutics, University of Florida and Geriatric Research Education & Clinical Center, Malcolm Randall Veterans Affairs Medical Center; Morgan D. Department of Psychiatry, University of Florida, Gainesville, FL. Rationale: We have previously demonstrated that the chronic administration of leptin antagonist to the ventral tegmental area (VTA) results in significant increases in food consumption and consequent body weight increases. The primary question examined here was whether this increased food consumption was accompanied by an increased motivation to obtain high-sugar and/or high-fat pellets in an operant conditioning situation using a progressive ratio schedule of reinforcement. Methods: F-344xBN male rats (3 months old) were either fed ad lib and allowed to eat regular chow (n=10), or maintained at ~85% free-feeding body weight and trained to respond in operant chambers for high sugar or high fat food pellets (n=16). Once behavior was stable, we used recombinant adeno-associated virus (rAAV)-mediated gene delivery by microinjection to the VTA to overexpress a mutant of rat leptin, yielding a protein that acts as a dominate-negative antagonist of the leptin receptor or a control GFP vector. Responding maintained by high-sugar and high-fat pellets was assessed under a variety of feeding conditions: maintained at ~85% free-feeding body weight, "matched" feeding where the control animals were fed similar levels as the leptin antagonist animals, and free-feeding conditions. Results: Ab lib fed, leptin-antagonist animals became obese as evidenced by a transient increase in FI (151 ± 7 vs. 127 ± 8 g, cumulative from days 13-20, $p<0.05$) and steadily increased delta body weight over the course of 67 days (weight gain at day 67: 39 ± 7 vs 15 ± 4 g, $p<0.02$), that was primarily accounted for by increases in body fat rather than lean mass. In the operant-trained rats, responding was maintained by a progressive-ratio schedule of reinforcement with high sugar- and high fat-pellet as the reinforcers. Food-maintained behavior across all experimental conditions was similar for leptin-antagonist and control treated animals. Conclusions: Chronic leptin antagonist administration to the VTA alters consumption of regular chow food ("liking"), however it fails to alter the motivation to obtain desirable foods ("wanting"). Supported by the NIH DK091710 and the Medical Research Service of the Department of Veterans Affairs.

23. **The effects of immune system stimulation on toxin (LiCl)-induced conditioned place avoidance in the female rat.** Cloutier, C.J. University of Western Ontario; Kavaliers, M. University of Western Ontario; Ossenkopp, K.P. University of Western Ontario. This study examined the effects of immune system stimulation, at the peri-pubertal stage and/or adulthood, on the acquisition of toxin (LiCl)-induced conditioned place avoi dance (CPA). At 42 days old, 64 female Long Evans rats were intraperitoneally (ip) injected with either the bacterial endotoxin lipopolysaccharide (LPS; 200 µg/kg), or 0.9% isotonic saline (NaCl; 1 ml/kg) and returned to the home cage. At approximately 60 days old (adulthood), all animals underwent place avoidance conditioning that consisted of two training cycles

that were 4 consecutive days each, spaced 72 h apart. On drug-paired conditioning days 1, 3, 7, and 9, animals were treated with LPS (200 µg/kg, 1 ml/kg) or 0.9% isotonic NaCl (1 ml/kg, ip) 90 minutes prior to a second ip injection of either 0.15M lithium chloride (LiCl; 15 ml/kg) or 0.9% NaCl (15 ml/kg), immediately followed by a 30 minute exposure to a specific context (gray wall, Perspex floor) and limited to the right chamber only. On control days 2, 4, 8, and 10, all animals were treated with 0.9% NaCl (1 ml/kg) 90 minutes prior to a second injection of 0.9% NaCl (15 ml/kg), immediately followed by a 30 minute exposure to a different context (striped wall, wire floor) and limited to the left chamber only. 72 hours following the final conditioning day, all animals underwent two consecutive drug-free test days, wherein they were permitted to explore either of the two chambers during a 20 minute period. The results of this study replicate prior findings showing that systemic LiCl conditions place avoidance in the rat, evidenced by significantly less time spent in the drug-paired chamber relative to saline controls on a drug-free test day. Furthermore, rats that were pre-treated with LPS 90 minutes prior to LiCl conditioning spent significantly more time in the drug-paired chamber relative to NaCl pre-treated rats that were conditioned with LiCl, showing that LPS impaired the acquisition of conditioned place avoidance. Treatment with LPS at the peri-pubertal stage did not have a significant effect on learning the CPA paradigm in adulthood, evidenced by a significantly shorter period of time spent in the drug-paired chamber relative to saline controls that was comparable to other LiCl-treated animals not treated with LPS at any time point. These results are also consistent with prior findings that show LPS blocks the conditioning of disgust responses (i.e., gaping behavior) in the rodent model of anticipatory nausea.

24. **Noradrenergic dysregulation of glutamate in the mPFC: A potential mechanism for cognitive dysfunction in rats exposed to chronic unpredictable stress.** Julianne D. Jett and David A. Morilak; Department of Pharmacology and Center for Biomedical Neuroscience, University of Texas Health Science Center at San Antonio. Stress-related neuropsychiatric illnesses, such as depression and anxiety disorders, are associated with deficits in cognitive flexibility. Cognitive flexibility, the ability to modify behavior in response to changes in the environment, depends on medial prefrontal cortex (mPFC) function. Previously we showed that chronic unpredictable stress (CUS) impairs cognitive flexibility in rats, assessed by the attentional set-shifting test. Adrenergic antagonists given locally in the mPFC prior to each CUS session protected cognitive flexibility (Jett and Morilak, 2013), suggesting that repeated noradrenergic activity during CUS is detrimental to mPFC function. Norepinephrine (NE) modulates glutamate neurotransmission in the mPFC. Thus, repeated NE activity over time may compromise glutamate neurotransmission in this region, resulting in cognitive deficits. To address this hypothesis, we first assessed CUS-induced changes in glutamate neurotransmission in the mPFC using microdialysis in male Sprague Dawley rats (250-280g) unilaterally implanted with microdialysis cannulae targeting the mPFC. They were exposed to 2 weeks of CUS or non-stressed control conditions. Twenty-four hrs after the last CUS treatment (Day 15), in vivo glutamate microdialysis was conducted. Following baseline samples, rats were exposed to 30 min of acute immobilization stress, then returned to their home cage for recovery samples. The level of glutamate in each sample was analyzed using high performance liquid chromatography. Acute immobilization stress significantly increased glutamate levels in the mPFC of non-stressed control rats, but the glutamate response to acute immobilization stress was significantly attenuated in CUS-treated rats. These results suggest that chronic stress dysregulates glutamate neurotransmission in the mPFC. Studies are ongoing to evaluate the role of NE in this diminished response by administering a cocktail of α1-, β1-, and β2- adrenergic receptor antagonist into the mPFC prior to each CUS session, then conducting glutamate microdialysis with immobilization stress on Day 15. We anticipate that local antagonist treatment during CUS will prevent CUS-induced changes in glutamate neurotransmission in the mPFC. By elucidating the mechanisms that link chronic stress to PFC 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.

25. **Potential therapeutic target for adult ADHD: D4 receptor agonist (A-412997) improves performance in the 5C-CPT in a rat model of the inattentive subtype of adult ADHD.** Tomlinson. A, Marshall. KM, Neill. JC (Pharmacy School, University of Manchester, Manchester, UK). The dopamine D4 receptor has been widely implicated as a genetic risk factor for ADHD making it an important target for pharmacological intervention. The aim of this study was to test the effects of the selective D4 receptor agonist; A-412997 on vigilance, sustained attention and response inhibition, using the 5-choice continuous performance task (5C-CPT) in rats separated into high (HA) and low (LA) attentive subgroups. Adult female Lister-hooded rats (n=20) were trained for approximately 24 weeks in the 5C-CPT. They were then separated into subgroups (HA, n=8; LA, n=8) on the basis of baseline individual differences in sustained attention, vigilance, and response disinhibition in the 5C-CPT. The LA subgroup was selected to represent the inattentive subtype of adult ADHD. Subsequently, the effects of the D4 selective agonist A-412997 were assessed in LA and HA subgroups. All animals received A-412997 (0.1, 0.3, 1.0 umol/kg; i.p) or vehicle (0.9% saline i.p.) 30 min prior to testing. Animals were challenged on test days by increasing the inter-trial interval (ITI) from 5 s to 10 s. 1) Two subgroups were formed: low-attentive (LA) and high-attentive (HA). LA animals scored significantly lower in terms of accuracy (sustained attention) ($p<0.001$), sensitivity index (SI) ($p<0.001$); a measure of vigilance, and false alarm responding ($p<0.001$); measure for response inhibition, under baseline conditions in the 5C-CPT. 2) Subgroups were differentially affected by A-412997. A-412997 improved performance in LA animals and had no effects on HA animals. In LA animals A-412997 (0.3 and 1.0 umol/kg) significantly decreased correct rejections ($p<0.01$, $p<0.001$; respectively) and decreased false alarm responding ($p<0.01$, $p<0.001$; respectively). The same doses also increased the SI indicating an increase in vigilance ($p<0.05$, $p<0.01$; respectively). This is the first study using adult rats to demonstrate the usefulness of the 5C-CPT to select subgroups modeling the inattentive subtype with deficits in response inhibition of adult ADHD. These results show that LA rats are more sensitive to D4 receptor agonism than HA rats, demonstrated by improved vigilance and response inhibition only in the LA animals. These data support the use of this LA ADHD model to investigate the inattentive subtype in adult ADHD. This is an important paradigm for increasing the understanding of the physiologic underpinnings of adult ADHD-subtypes and treatment responses.

26. **Role of nucleus accumbens in generation of 50 kHz vocalizations induced by systemic amphetamine.** Mulvihill K. G. and Brudzynski S. M., Department of Psychology, Brock University, St. Catharines, ON, Canada. It has been established that rats emit 50 kHz vocalizations, as a signal of appetitive state, after pharmacological activation of the mesolimbic dopamine system for example by amphetamine. Previous studies have suggested that the shell of nucleus accumbens is a critical structure for induction of 50 kHz vocalizations in this species. Thus, the question arises whether lesions of the shell of the accumbens blocks production of 50 kHz calls after systemic application of amphetamine. Twelve Long Evans rats were stereotaxically implanted with intraaccumbens cannulae for placement of reversible lesions with procaine (25 μg in 0.5 μl per injection). The shell of the nucleus accumbens was bilaterally injected with procaine or saline before systemic application of d-amphetamine (2 mg/kg). The lesions had no significant effect on the acoustic parameters of vocalizations, or no effect on the proportion of basic subtypes of 50 kHz calls (flat, trills, complex calls). Only the proportion of the step-up (but not step-down) calls differed between saline and procaine conditions. It is concluded that the shell of the nucleus accumbens might not be a critical structure for production of 50 kHz vocalizations but part of the more extensive mesolimbic system. This research was supported by Natural Sciences and Engineering Research Council of Canada.

27. **Anterior cingulate cortex inactivations increase reward expectancy on a rodent slot machine task.** Cocker, P. J., Hosking, J. G & Winstanley, C. A. Department of Psychology. University of British Columbia. Gambling is a growing public health concern, and treatment options for pathological

gambling remain extremely limited and of questionable efficacy. Cognitive theories of gambling suggest the transition from recreational to problematic gambling is due to cognitive biases or distortions. One of the most well characterised of these biases are 'near-miss' effects. 'Near-misses' are unsuccessful outcomes that are proximal to a win, such as matching two items on a slot machine payline and the third just missing. Although near-misses are present throughout multiple forms of gambling, they are particularly prevalent in slot machines, and indeed are purportedly one of the major reasons why slot machines represent such a virulent form of gambling. Near-misses are thought to promote prolonged game play by fostering beliefs of mastery and generating reward expectancy, even in the absence of reward. Human imaging studies have showed robust activation of the anterior cingulate cortex (ACC) during slot machine play and evidence suggests a role for the ACC in biasing choice towards a prepotent but sub-optimal response. Taken together, this suggests that ACC activation may underlie the ability of 'near-misses' to evoke reward expectancy in human gamblers. Using animal models we may be better able to elucidate the neurobiological basis of these cognitive biases and thus develop novel treatment options. We have developed a rodent slot machine task using standard operant chambers that suggests rats, like humans are susceptible to the putative wining signals conveyed by non-winning, near-miss trials. Here, we show that inactivations of the ACC increase animals' erroneous expectations of reward on non-winning trials. This data suggests that the ACC may be critically involved in generating reward expectancy in response to winning signals within non-winning outcomes on slot machines

28. **Reproduction and maternal experience alter neuroplasticity in the midbrain dorsal raphe.** Holschbach MA, Lonstein JS; Neuroscience Program, Michigan State University. The transition to motherhood brings about dramatic alterations to a female's physiology and socioemotional behaviors. This transition is driven by changes in the mother's endocrine status that elicit widespread neural plasticity. The birth and development of new brain cells has been studied in several regions of the peripartum forebrain, where reproductive state and maternal interactions with pups affect cytogenesis, but the midbrain has never been investigated. In this study, we investigated cytogensis in the dorsal raphe, the brain's main source of serotonin. Serotonin affects lactation and various aspects of postpartum socioemotional behaviors, so neuroplasticity within the dorsal raphe could play a vital role for new mothers. Using bromodeoxyuridine (BrdU; 150 mg/kg) to label mitotic cells in virgin, pregnant, and postpartum rats, we recently discovered that reproductive state affects cytogenesis in the dorsal raphe, with cells born one week after parturition less likely to survive than cells born during pregnancy. To begin to investigate mechanisms underlying the postpartum reduction in cytogenesis, we first examined whether removing pups immediately after birth would increase the survival of new cells. Using BrdU to label mitotic cells in postpartum females with or without their pups, we found that interacting with pups significantly reduced survival of new cells in the dorsal raphe. To determine if pup presence reduced cell survival by increasing the dams' circulating corticosterone levels, an ongoing experiment will assess whether adrenalectomy increases cell survival in the dorsal raphe of dams with their pups and whether replacement of corticosterone prevents this effect. Lastly, to determine possible functional significance of this change in cytogenesis, we are currently examining serotonin content in the dorsal raphe across reproductive state and in dams with or without pups. Research into serotonergic neuroplasticity underlying the normal postpartum changes in behavior and physiology could help identify novel targets for ameliorating postpartum emotional disorders and facilitate interactions between mothers and their infants. Furthermore, this work is the first demonstration of cytogenesis in the midbrain dorsal raphe of any adult mammal and has implications for emotional and other behaviors involving the serotonergic system even outside the peripartum period.

29. **Differential expression of Fos-family protein in the maternal and non-maternal brain.** Ragan CM, Michigan State University; Holschbach MA, Michigan State University; Robison AJ, Michigan State University; Lonstein JS, Michigan State University. The peripartum period includes numerous

neurochemical changes in the female mammalian brain that alter their behavior. During this time, females switch from aversion to attraction to pups. However, the neuronal and hormonal mechanisms contributing to this behavior are not entirely clear. Serotonin pathways play a role in maternal behavior, but its molecular regulation of these behaviors is unknown. FosB proteins, which are markers of chronic stimulation, act as a molecular switch and may regulate serotonin mechanisms involved in maternal behavior. We are currently investigating the effects of maternal state on protein expression of FosB, and two of its isoforms, ΔFosB and Δ2Δ FosB, in a major source (dorsal raphe) and three targets (medial preoptic area, bed nucleus of the stria terminalis, and nucleus accumbens) of the brain's serotonin system. To do so, we examined the brains of diestrus virgins, postpartum day (PPD) 7 females, and PPD 19 females. To further investigate the effect of maternal experience, we will soon measure FosB protein expression in PPD 7 females that had pups removed on the day of parturition and PPD 7 females that remain with pups until sacrifice. Lastly, we will quantify FosB protein expression in virgin females that were repeatedly exposed to pups during a nine-day period in a pup sensitization paradigm where some females showed maternal behaviors, while others did not. We hypothesize that differential ΔFosB protein expression may be part of the "molecular switch" from aversion to pups to attraction to pups in sensitized virgins and early postpartum females. Specifically, if ΔFosB is relevant for maternal behavior, it may increase early in the postpartum period then decline as lactation ends. In addition, compared to PPD 7 females that had pups removed at parturition, PPD 7 females that remained with pups may express more ΔFosB in our targeted brain regions, and chronic pup contact may increase ΔFosB expression in these females. Similar to what has been shown for previous work on chronic drug exposure, FosB proteins may be also important components of the molecular mechanisms involved in the onset of maternal behavior.

30. **GABA(B) receptor signaling and behavioral flexibility in aging.** Beas, B.; Banuelos, C.; Gilbert, R.; Setlow, B.; Bizon, J. Departments of Neuroscience, University of Florida, College of Medicine, Gainesville, FL. The ability to flexibly modify behavior in response to changing 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. Notably, experimental manipulations that model schizophrenia demonstrate that altering prefrontal cortical excitability can impair behavioral flexibility. Moreover, our laboratory previously reported an age-related decline in expression of prefrontal cortical GABA(B) receptors which mediate tonic inhibition in this brain region. Experiments in the current study were designed to determine if reduced GABA(B)R expression in aging is associated with deficits in behavioral flexibility and if modulation of these receptors can enhance flexibility in young and aged rats. In experiment 1, adult (5 mo.) and aged (21 mo.) male F344 rats were behaviorally characterized on an attentional set-shifting task that assesses behavioral flexibility. In this task, rats initially learned to perform a simple visual discrimination task. After reaching criterion performance, the reward contingencies were "shifted" such that rats had to ignore the cue light and discriminate between the levers on the basis of their left/right position. Both young and aged rats acquired the initial discrimination similarly; however, aged rats were impaired relative to young following the set shift. Notably, there was significant variability in the presence and degree of impairment among aged rats. Western blotting performed on homogenates of prefrontal cortex from these behaviorally characterized rats indicated that GABA(B)R expression in aged prefrontal cortex strongly predicted performance on the set shifting task, such that less GABA(B)R expression was associated with worse performance. Experiment 2 tested whether baclofen, a GABA(B)R agonist, could enhance set-shift performance. Naïve young and aged rats received i.p. injections of various doses of baclofen (vehicle, 1.0 and 2.5 mg/kg) prior to the 'set-shift' component of the task. In both young and aged rats, set-shifting performance was significantly and robustly enhanced by 2.5 mg/kg baclofen relative to vehicle and 1.0 mg/kg baclofen. Together, these data suggest that attenuated GABA(B)R

signaling contributes to age-related deficits in behavioral flexibility. Supported by AG029421 (JLB), McKnight Brain Research Foundation and NSF GRFP DGE-0802270 (SB).

31. **The role of hippocampal G-protein coupled estrogen receptor in social recognition and object recognition learning in the absence of spatial cues in female mice.** Lymer, J.;Gabor, C.; Phan, A.; Young-MacDonald, F.; Morris, H.; Choleris, E. Psychology and Neuroscience, University of Guelph. Estrogens can rapidly improve performance on different learning and memory tasks, including social recognition, object recognition, and object placement (Phan et al. 2011, 2012). These tasks have been improved with both systemic and intrahippocampal administration of 17β-estradiol, an estrogen receptor (ER) α agonist, or a G-protein coupled estrogen receptor (GPER) agonist. These tasks were completed within the test mouse home cage where there are various cues that can help identify stimuli. Subsequent investigations with a Y-apparatus, designed to eliminate most of the spatial and contextual cues, assessed whether enhancing effects in the recognition paradigms were direct or facilitated via the spatial aspects of these tasks. Intrahippocampal (CA1) administration of 17β-estradiol improved object but not social recognition in the Y-apparatus, suggesting that ERs in the hippocampus can facilitate object recognition without the influence of spatial and contextual cues. However, systemic administration of 17β-estradiol did improve social recognition in the Y-apparatus suggesting that brain regions outside the hippocampus facilitate estrogen's enhancing effects on social recognition. 17β-estradiol acts on 3 main ERs and home cage tests have shown that intrahippocampal ERα and GPER agonists improve social recognition whereas an ERβ agonist impairs it. The current study investigates the role of the relatively recently discovered GPER in the hippocampus specifically in object and social recognition in the absence of spatial cues. The GPER agonist, G-1 (50nM, 100nM, 200nM; 0.5μL at rate: 0.2μL/min) was infused directly into the CA1 region of the hippocampus and the ovariectomized mice were tested on either object or social recognition in the Y-apparatus. Testing begun 15 minutes post-infusion and consisted of 2 habituations and one test, each 5 min in duration, at 5 min intervals, hence testing was completed within 40 minutes of drug administration. Two objects or ovariectomized conspecifics were used, and at test one of the two stimuli was replaced with a novel one. The social recognition experiment is underway. Object recognition results show improvement with both 50nM and 200nM G-1, suggesting that GPER in the hippocampus is able to facilitate object recognition even in the absence of most spatial and contextual cues. Thus, the mouse hippocampus seems involved in object recognition and estrogens can mediate this function via action at GPER. Supported by NSERC.

32. **Modulation of male social behaviors by parathyroid hormone 2 receptor expression in the medial amygdala.** Tsuda, M. Section on Fundamental Neuroscience, NIMH, NIH, Bethesda, MD, USA; Usdin, T. Section on Fundamental Neuroscience, NIMH, NIH, Bethesda, MD, USA. Psychopathologies related to social interaction are a significant social problem. Therefore, it is important to understand the biopsychological and neurobiological processes underlying such disorders. While examining the phenotype of male mice with null mutation of the parathyroid hormone 2 receptor (PTH2R-KO), we observed considerably increased investigatory behavior toward same sex adult mice in a social investigation test (SIT), but decreased levels of aggression. The PTH2R is expressed by neurons in several areas involved in social behavior, including the medial amygdala (MeA). These areas receive projections from neurons synthesizing its ligand, the neuropeptide tuberoinfundibular peptide of 39 residues (TIP39). As TIP39 and PTH2R are present in many brain regions, we asked whether TIP39 signaling in the MeA has a significant role in male social behaviors. The MeA of WT male mice was bilaterally stereotaxically injected with a virus encoding a secreted PTH2R antagonist (HYWH) and GFP that marks infected cells, or one encoding GFP only (control), and SIT was performed 5 wk later. Similar to the KO results, HYWH injected mice exhibited increased social investigation toward a same sex stimulus animal, compared to controls. To further define the anatomical location and relevant time of TIP39 signaling, male mice that express Cre-recombinase in PTH2R neurons were stereotaxically

injected with a virus encoding a Gi-coupled Cre-dependent receptor exclusively activated by clozapine-N-oxide (CNO). We targeted the MeA or bed nucleus of the stria terminals (BNST). Five weeks later, saline or CNO, was administered 1 hr before SIT. We found that inhibiting PTH2R neurons in the MeA at the time of SIT increased social investigative behaviors toward another male mouse, but inhibition of BNST PTH2R neurons had no effect, compared to saline treated mice. These results collectively suggest that TIP39 signaling in the MeA contributes to the modulation of male social investigatory behavior. We are currently investigating whether these modifications are due to changes in neuroendocrine functions that regulate male social behaviors or altered cognitive processing of conspecific odors. The PTH2R is expressed by a circumscribed MeA neuronal population, so this work may lead to refinement of circuits thought to regulate social behavior or identification of a novel circuit specific regulating social behavior.

33. **Effects of Striatal Lesions on Reward Choice Using a Multi-box Environment.** Joshua M. Ricker, Richard Kopchock, Justin Hatch, Christina Downey, Howard C. Cromwell, Department of Psychology, Bowling Green State University, Bowling Green, OH, 43402. Making an advantageous choice between multiple rewards requires an organism to properly and efficiently assign value to each option. Factors such as magnitude of reward, time of delivery, and effort put forth must be taken into account. The ventral and dorsal subsections of the striatum have been shown to play a critical role in this process. Uncertainty exists in linking the striatal subregions to specific processes involved in decision-making and choice behavior. While there has been much work done investigating the role of these brain areas on reward choice and decision making, this research has been limited because it has required extended training, and included limited freedom of choice. The current study employs a novel testing apparatus that consists of a middle "decision" box, which is connected to two boxes with differing food reward magnitudes. One box (the constant box) would be associated with a reward of constant value, while the other would be associated with a varying reward value (the variety box). Rats received quinolinic acid lesions to the dorsal striatum, ventral striatum, or sham lesions and were tested using this novel apparatus. They had the choice between constant versus variable reward options. The reward option varied in terms of food amount available, and during a 6-week period, varied in terms of the extent of magnitude differences for each option. The different pellet options included: week 1: constant box = 0, variety box = 0/3; week 2: constant box = 1, variety box = 0/3; week 3: constant box = 2, variety box = 0/3; week 4: constant box = 1, variety box = 0/5; week 5: constant box = 1, variety box = 0/3; week 6: constant box = 1, variety box = 0/1. This new apparatus also allows for multiple dependent measures to be recorded. These include: food cup checks, total time in box, number of rewards obtained, and ultrasonic vocalizations. Preliminary data suggests that relative reward processing during choice behavior differs between control-sham and animals with lesions. This novel design may allow for a fresh perspective on testing reward choice, and it may lead to a better understanding of psychiatric disorders ranging from substance abuse to anxiety disorders.

34. **Intermittent access to a cafeteria-type diet affects feeding behavior of female marmoset monkeys.** Borges, A.C.; Duarte, R.B.M.; Bomfim, P.C.B.; Costa, J.R.; Barros, M. Primate Center and Dept. of Pharmaceutical Sciences, University of Brasilia, DF 70910-900 Brazil. Intermittent access to a highly palatable diet induces, over time, an increase in consumption of such items by rodents, corresponding to a binge-type behavior. We tested whether a highly palatable cafeteria-type diet (CD) could similarly alter the feeding pattern in non-food deprived adult female marmoset monkeys (Callithrix penicillata). On three consecutive days, 30-min home-cage observation sessions determined baseline-feeding patterns of their first meal of the day. Animals had access only to their normal diet (ND) of fresh fruit and chow. Then, twice a week and in a separate feeding-chamber, each female received for 30-min CD plus fruit as its first meal. CD consisted of a mixture of M&M chocolate, oreo cookies, mozzarella cheese and cocoa puffs. At all other times, subjects were kept in their home-cages with access only to their ND. After a 7-week period, home-cage baseline-feeding patterns of the ND were re-analyzed

during three 30-min sessions held 24 h apart. Although a significant overall escalation in CD intake was not observed, within-group variation was high. Marmosets were thus divided into 'Prone to Overeat' or 'Not-Prone to Overeat', with the former ingesting significantly more total calories on their first and last CD+fruit meals in the feeding-chamber, compared to the latter group and their own pre- and post-CD intake levels (i.e., home-cage baseline). Differences in calorie ingestion were due solely to a significantly higher CD intake by the 'prone to overeat' females. In fact, baseline home-cage ingestion of the ND was equivalent between groups and remained the same before and after exposure to the CD. A similar profile was seen for the time spent foraging, while locomotion and body weight, in general, remained constant. Therefore, even though adult female marmosets did not escalate consumption of high-fat/sugar foods over time – as seen in rodents – some seemed naturally prone to overeat a CD. Differences in terms of life span, variety of items normally consumed and hedonic value of palatable foods may possibly account for the species differences presently observed. Supported by CNPq (478930/2012-7 and 303331/2012-7) and FAP-DF (193.000.408/2010).

35. **Chocolate induces a conditioned-place-preference response in a nonhuman primate.** Duarte, R.B.M.1; Patrono, E.2,3; Borges, A.C.1; Mitri, S.C.1; César, A.A.S.1; Tomaz, C.1; Ventura, R.2,3; Gasbarri, A.2,3; Puglisi-Allegra, S.3,4; Barros, M.1 1 Primate Center, University of Brasilia, 70910-900, Brazil; 2 Dept. of Applied Clinical and Biotechnological Sciences, University of L'Aquila, 67100, Italy; 3 European Center for Brain Research, Santa Lucia Foundation IRCCS, Rome, 00143, Italy; 4 Dept. of Psychology, University of Rome La Sapienza, 00185, Italy. Highly palatable foods – with high fat/sugar content – may induce an addiction-related response similar to that seen for drugs of abuse. However, this has yet to be fully characterized in nonhuman primates. So, we tested whether adult marmoset monkeys (Callithrix penicillata) develop a place-preference response conditioned to repeated consumption of chocolate. Subjects were first submitted to three 15-min habituation trials in a two-compartment CPP box and then randomly assigned to a chocolate (CHOCO) or control group (CTRL). Marmosets were subsequently submitted to twelve 15-min conditioning trials in the CPP box, held at 24 h intervals. On odd-numbered days (i.e. 1, 3, 5, 7, 9 and 11) the CTRL group received regular chow while the CHOCO group received chocolate in one of the compartments. On even-numbered days (i.e. 2, 4, 6, 8, 10 and 12), both groups received chow in the other compartment. A single 15-min test trial was held 24 h after the last conditioning session, during which subjects had free access to both compartments in the absence of any food reward. During the initial habituation, use of space within the CPP box was homogenous for all subjects. At the end of the conditioning trials, marmosets from the CHOCO group had consumed significantly more chocolate than chow, whereas CTRL animals ingested equivalent amounts of chow in both compartment and at levels similar to those of the former group. Time spent foraging, however, did not differ between groups or compartments. On the test trial, marmosets from the CHOCO group spent significantly more time in the chocolate-paired compartment, compared to their pre-conditioning levels and to CTRL subjects. Use of space by these marmosets remained as seen prior to conditioning (to chow). Therefore, the consumption of chocolate induced a response profile in the marmoset monkeys that corresponds to a place-preference effect, similar to previous reports in rodents and that of classical drugs of abuse. Supported by CNPq (478930/2012-7 and 303331/2012-7), FAP-DF (193.000.408/2010) and CAPES.

36. **Differential effects of pharmacological and restraint stress on effort-based decision-making.** Bryce, C. University of British Columbia; Floresco, S. University of British Columbia. 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 in turn may reduce the tendency to exert effort to obtain rewards. The goal of the present study was to examine the effects of different types 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 increases in corticosterone, causes rats to choose the HR option less compared to baseline performance. In a subsequent study, we assessed the effects of the alpha 2 adrenoreceptor antagonist yohimbine (1-3 mg/kg, IP), which mimics increased noradrenaline transmission induced by acute stress, on effort-based decision-making. Our expectation was that yohimbine would decrease choice of the HR option, in a manner comparable to restraint stress. In stark contrast to our expectations, we found that yohimbine increased preference for the HR option compared to vehicle treatment. This suggests that yohimbine and restraint stress produce divergent effects on some decision-making tasks, highlighting the fact that different types of stressors can induce opposing effects on behavior. Whether other neurochemical changes associated with acute stress, such as increases in corticotropin-releasing factor (CRF), mediates an increase in effort discounting is a topic for future research.

37. **Dopamine in the basolateral amygdala modulates choice during risk/reward decision making.** Larkin, J. Department of Psychology, University of British Columbia. Floresco, S. Department of Psychology, University of British Columbia. Different aspects of cost/benefit decision making involving uncertain rewards are facilitated by corticolimbic circuits linking regions of the prefrontal cortex, ventral striatum and basolateral amygdala (BLA). Dopamine (DA) also plays an integral role in promoting choice of larger, uncertain rewards; manipulations of DA transmission the PFC or nucleus accumbens alters risky choice. Considerably less is known about how BLA DA regulates risk-based decision making. The present study assessed the effects of DA receptor antagonism within the BLA on risk-based decision making, assessed with a probabilistic discounting task. Rats were trained to choose between a small/certain lever (1 reward pellet) and a large/risky lever (4 pellets) delivered in a probabilistic manner. The odds of obtaining the larger reward decreased or increased in a systematic manner across 4 blocks of discrete-choice trials (100-12.5% or 12.5-100%) during a daily session. In well-trained rats, blockade of BLA D1 receptors via infusions of SCH23390 increased discounting of the larger/uncertain reward and reduced risky choice, in a manner similar to D1 receptor antagonism within the medial prefrontal cortex or nucleus accumbens. In contrast, intra-BLA D2 blockade with eticlopride did not affect overall choice, but did reduce reward sensitivity, as reflected by a decrease in win-stay behavior. These findings, in combination with previous data suggest that D1 receptors in multiple DA terminal regions, including the BLA have an important role in facilitating optimal decision making and promoting choice of larger/uncertain rewards. More generally, these findings highlight a key contribution by mesoamygdala DA in regulating certain aspects of cost/benefit decision making, with D1 activation promoting bias towards risky choices, and D2 receptors providing short-term feedback about recently rewarded actions. These findings may have important implications for understanding mechanisms underlying alterations in decision making and reward processes in psychiatric disorders linked to dysfunction of the amygdala and DA system.

38. **Hippocampal glucocorticoid and mineralocorticoid receptor responses to acute and repeated restraint stress exposure in male and female rats.** Innala, L. University of British Columbia; Viau, V. University of British Columbia. Female rats typically display higher plasma concentrations of corticosterone (CORT) than males under basal conditions, as well as in response to acute challenges. We recently compared CORT responses in male and female rats exposed to single or repeated episodes of 3h restraint, repeated daily for 5 consecutive days. Male and female rats showed significant declines in CORT responses between the first and last day of restraint exposure. However, the magnitude of the CORT response on the final day of testing remained significantly higher in females compared to males.

Based on this finding we reasoned that there might be a sex difference in glucocorticoid-mediated, negative feedback regulation of the HPA axis. Using Western blot analysis, we assessed mineralocorticoid and glucocorticoid receptor (MR and GR) responses in dissected hippocampus of animals exposed to acute and repeated restraint. There was a main effect of repeated restraint to decrease whole cell levels of hippocampal GR and MR in both males and females. Analysis of receptor distribution revealed a decrement in the nuclear translocation of the GR in the repeat restraint condition, comparable between male and female rats. In contrast, there was a tendency for increased MR translocation following repeated restraint in females, but not in males. Prompted by these findings to suggest potential interactions between stress-HPA axis habituation and sex on GR and MR responses, we are currently expanding our analysis to include additional time points and other brain regions known to mediate negative feedback regulation of the HPA axis.

39. **A novel inter-temporal choice task.** Marci R. Mitchell, Nathaniel J. Smith, Daeyeol Lee, & Jane R. Taylor Department of Psychiatry, Yale University School of Medicine. Delay discounting describes the process by which the value of a large reward is discounted as the time to reward receipt becomes farther into the future. In both humans and animals, delay discounting during inter-temporal choice tasks typically takes the form of hyperbolic discount function. By contrast, in most previous rodent studies on delay discounting, only the large reward was delayed, and as a result, evidence for or against hyperbolic discounting was not conclusive. Here, we have developed an inter-temporal choice task more analogous to that used in humans for rodent. Methods: 14 male Long-Evans rats (beginning at 250-300g) were trained in the inter-temporal choice task in which they were given choices between two response levers, the first which delivered a small, single pellet food reward and the second which delivered a large, two pellet food reward (counterbalanced across operant chambers). Choices were given in blocks of 12 discrete trials. Delays on either lever vary between 0 and 32 s. Results: The animal's preference for the large reward was systematically influenced not only by the delay for the large reward, but also by the delay for the small reward. We are currently investigating whether the animal's preference can be modeled more accurately by exponential vs. hyperbolic discount functions. Conclusions and Future Directions: We successfully trained rats to perform a novel inter-temporal choice task. We are currently testing a model in which delay sets are presented in a randomized order to further model inter-temporal choice tasks. Additionally, we are determining the effects of acute and chronic drugs of abuse on choice behavior during inter-temporal choice. We expect that certain substances will alter the rate and or shape of temporal discounting.

Thursday, June 12

8:00-10:00 **Symposia: Warm feelings, warm thoughts: Thermosensation, emotional behavior, and mental health.** Chair: Christopher A. Lowry

Disruption in body temperature diurnal rhythms predict stress sensitization. Monika Fleshner and Robert Thompson; University of Colorado Boulder. Using an animal model designed to produce physiological symptoms (i.e., stress sensitization) found in patients suffering from post-traumatic stress disorder (PTSD), we investigated the hypothesis that disruptions in thermoregulation may precede and predict the development of stress sensitization. Adult male F344 rats implanted with biotelemetry devices were exposed to repeated conditioned fear or control conditions for 22 days followed by either no, mild, or severe heterotypic acute stressor exposure on day 23. Core body temperature (CBT) was biotelemetrically monitored continuously throughout the study. Rats exposed to repeated fear had fear-evoked increases in behavioral freezing and CBT during exposure to the fear environment and expressed physiological indices of chronic stress. Repeated fear flattened CBT rhythms due to primarily an elevation of CBT during the light/inactive cycle. Repeated fear also produced sensitized CBT responses following acute stress, relative to the effect of acute stress in the absence of a history of repeated fear. A sensitized physiological stress response is a hallmark of PTSD. Greater disruptions of diurnal rhythms during repeated fear predicted sensitized acute stress-induced physiological responses. The results suggest that chronic stressors can produce diurnal rhythm disruptions consistent with a potential dysregulation of thermoregulatory cooling systems; and such changes may help predict sensitized physiological stress responses following traumatic events. Monitoring diurnal disruptions in CBT during repeated stress may thus help predict susceptibility to PTSD.

That warm fuzzy feeling: warm temperature activates brain serotonergic systems and has antidepressant-like effects in rats. Christopher A. Lowry, University of Colorado Boulder, Department of Integrative Physiology and Center for Neuroscience, Boulder, CO, 80309-0354, USA. Studies in the 1970's revealed that environmental warming activates putative serotonergic neurons in the midbrain raphe nuclei, a finding that could have major implications for understanding interactions between thermoregulation and emotional behavior. However, an influential study in 1987 concluded that serotonergic neurons in the dorsal raphe nucleus (DR), a major source of serotonergic innervation of forebrain limbic structure, were not thermosensitive. This finding dampened interest during the last 25 years in the potential role of serotonergic neurons in the brain as thermosensors. However, these conclusions were based on recordings from relatively few neurons. It remains possible that a subset of serotonin neurons is thermosensitive. We have found that subsets of brain serotonergic neurons are indeed sensitive to warm ambient temperature exposure in vivo and in vitro. Detailed analysis revealed that warm ambient temperature exposure activates subsets of serotonergic neurons within the DR implicated in stress resistance or antidepressant-like behavioral responses, but not subsets of serotonergic neurons implicated in facilitation of anxiety-like behavioral responses. Based on these findings, we predicted that exposure to warm ambient temperature could have antidepressant-like behavioral effects in rodent models. Rats were treated with a behaviorally inactive dose of the selective serotonin reuptake inhibitor citalopram or vehicle, and exposed to warm ambient temperature (37 degrees C) or room temperature for 85 min using a 2 x 2 experimental design. In rats pretreated with a subthreshold dose of citalopram, exposure to warm ambient temperature increased swimming, an antidepressant-like behavioral effect, without affecting climbing in the forced swim test. Core body temperature before and after the forced swim test was correlated with swimming behaviors. Together, these studies demonstrate that exposure of rats to warm temperature activates brainstem serotonergic systems and has antidepressant-like behavioral effects. Dr. Lowry will discuss potential neural mechanisms involved including activation of the recently characterized warm-sensitive spinoparabrachial pathway.

Warm feelings, interpersonal warmth: Cutaneous heating promotes interpersonal warmth. Matthew W. Hale, School of Psychological Science, La Trobe University. "Warmth" is a powerful personality trait in social judgement, and the 'warm-cold' dimension is one of the most important components of the first impressions that we form of others. Recent evidence has demonstrated that exposure to warm physical stimuli, like holding a warm coffee cup, can profoundly alter our perceptions of another person's psychological warmth. Meanwhile, our previous preclinical experiments in rats have demonstrated that local skin warming activates subpopulations of serotonergic neurons that are known to decrease sympathetic nervous system (SNS) activity and alter emotional behaviour. Accordingly, we aimed to investigate if interaction with warm physical temperature can alter the perception of psychological warmth of a target person as well as decrease SNS activity in response to a mild stress stimulus. In this experiment, participants were recruited under the cover story of an investigation of the relationship between consumer healthcare products, personality types and responses to stress. Participants provided a baseline saliva sample and were then handed a Surgipack® Soft Hot/Cold Pack at either 37 °C (warm condition) or 0 °C (cold condition). Participants were asked to evaluate the effectiveness of the product, and were then asked to rate the typical user of this product on ten personality traits using bipolar scales anchored by a trait and its opposite, for example; serious and carefree. Half of the personality traits were semantically related to the warm-cold dimension, and half were unrelated. Participants were then asked to perform the short mental arithmetic component of the Trier Social Stress Test and provided a final saliva sample. Saliva samples were assayed for alpha amylase activity as a measure of SNS activity. Our results demonstrated that holding the hot/cold pack warmed to 37 ºC increased the perception of interpersonal warmth and inhibits sympathetic function. Furthermore, ratings of prosocial behavior were negatively correlated with measures of sympathetic activity. These data suggest that abstract psychological concepts, such interpersonal warmth are metaphorically based on physical experiences and linked with alteration in sympathetic responses to stress.

Warm feelings, warm thoughts: Whole body heating has rapid antidepressant effects in depressed patients. CL Raison, Department of Psychiatry, College of Medicine and College of Agriculture and Life Sciences, University of Arizona, Tucson, AZ. This talk focuses on research by our group suggesting that a single session of mild-intensity whole-body hyperthermia (WBH) may provide rapid and sustained improvement in depressive symptoms in patients with major depressive disorder (MDD). Our work using WBH in humans builds upon animal data that will be presented by other members of this symposium. Here we report on findings from a small open study of WBH in MDD conducted in Switzerland and on interim results from an ongoing randomized, double-blind, sham controlled study of WBH being conducted at the University of Arizona. In our first open study of 16 medically-healthy adults with MDD we observed that a single session of WBH induced a large-effect size reduction in depressive symptoms five days post-treatment that was sustained at 4 weeks post-treatment. Consistent with the possibility that WBH operates at least in part by sensitizing skin-to-brain thermosensory circuitry, WBH also reduced core body temperature, and reductions in core body temperature were correlated with reductions in depressive symptoms. Patients with elevated body temperature pre-treatment were observed to have more robust antidepressant responses. In our ongoing, sham-controlled study of WBH for MDD we report that active WBH has a large effect-size advantage over sham treatment for the reduction of depressive symptoms, commencing within 3 days of treatment and persisting for 4 weeks post-treatment in subjects receiving no other interventions. Preliminary evidence suggests that WBH may impact sleep and inflammatory mediators and that these effects may be associated with therapeutic effects. The presentation will conclude with a brief discussion of "next steps" in the evaluation of the potential utility of WBH for the treatment of mood and anxiety disorders.

8:00-10:00 **Symposia: Chronic stress and brain plasticity: Contrasting mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders.** Chair: Serge Campeau

Adapting to Stress: A Path of Most "Resistance". Campeau, S. Department of Psychology & Neuroscience, University of Colorado at Boulder, Boulder, CO, USA. Organisms, including humans, are bombarded by a multitude of daily physical and psychological challenges; yet most of these encounters fail to elicit significant responses that are routinely evoked by stressors. Various evidence suggests, however, that adaptation to repeated stressor exposure is dysregulated in depressed or anxious clinical populations. Such evidence may indicate that faulty brain mechanisms of adaptation contribute to the emergence of mood disorders in humans. This possibility is currently difficult to evaluate due to our poor understanding of the neural mechanisms of adaptation to stress. I will discuss our attempts at shedding light on putative brain regions that contribute to this important adaptive function, through the use of anatomico-functional procedures in a rat model of audiogenic stress habituation. I will also present the results of some of our most recent studies suggesting that adaptation to repeated stress appears to provide a key process in reducing the impact of later challenges (stress resistance). Together, these lines of research may provide new insights into the value and effectiveness of behavior therapy and new brain targets of interest associated with stress-related disorders.

Know when to take your chips off the table – acute stress adaptation begets chronic stress pathology. Morilak, D., University of Texas Health Science Center at San Antonio. Acute release of norepinephrine (NE) in many brain regions enhances adaptive behavioral and physiological responses to acute stress. But chronic or severe stress is a risk factor for many psychiatric disorders, including depression, schizophrenia, PTSD and other anxiety disorders. Impaired executive function is a component of many such disorders, specifically deficits of cognitive flexibility, the ability to modify established thoughts and behaviors in response to changes in the environment. Cognitive flexibility depends on the function of the prefrontal cortex (PFC), which is dysregulated in many stress-related npsychiatric disorders. We measure cognitive flexibility in rats using the attentional set-shifting test (AST). Chronic unpredictable stress (CUS) impaired cognitive set-shifting, and this deficit was prevented by chronic NE reuptake blockade. Alpha1 adrenergic receptors in mPFC facilitate set-shifting, and contribute to the beneficial antidepressant effect. These findings, and the fact that many antidepressants elevate noradrenergic tone, might suggest that stress-induced deficits in the modulatory function of NE contribute to the pathology of depression. However, we found that the acute release and modulatory influence of NE are not compromised after chronic stress. Thus, we hypothesized instead that the acutely adaptive modulatory effects of NE might become detrimental, contributing to cumulative PFC pathology if elicited repeatedly by chronic stress. In support of this hypothesis, we found that blocking adrenergic receptors in the mPFC during CUS protected against the cognitive deficit. More recently, we have begun to explore what in the PFC might be compromised by repeated noradrenergic facilitation during CUS. Acute release of glutamate in the mPFC in response to a mild acute stressor was attenuated after CUS, as was the induction of fos expression in the PFC in response to direct activation of the mediodorsal thalamus, a major glutamaterigic afferent. This response was also protected by adrenergic receptor blockade during CUS. Thus, it appears that repeated noradrenergic facilitation compromises both glutamate release and/or glutamate receptor signaling in PFC during chronic stress. Ongoing studies are now addressing the signaling mechanisms by which effective therapeutic strategies of different modalities (pharmacologic, behavioral, device-based) may restore glutamate function in PFC and rescue cognitive flexibility.

Medial prefrontal cortex involvement in adaptive and maladaptive responses to stress. Jason J. Radley, Ph.D., University of Iowa. A network of interconnected cell groups in the limbic forebrain regulate hypothalamic-pituitary-adrenal axis activation during emotionally stressful experiences, and disruption of these systems is broadly implicated in the pathophysiology of psychiatric illnesses. Whereas abnormalities in prefrontal cortical function help to explain many of the cognitive and behavioral aspects of stress-related mental illnesses, dysregulation of this cortical region has emerged as a key player in mediating neuroendocrine alterations following chronic stress. In this talk, evidence from our laboratory will be presented highlighting the neural mechanisms accounting for medial prefrontal cortical (mPFC) control over the HPA axis under acute stress conditions. Next, the effects of chronic stress, glucocorticoids, and aging on structural plasticity in mPFC

neurons will be described, with a discussion of how these alterations may lead to long-term behavioral and neuroendocrine consequences.

Stress and gonadal steroids: Implications for understanding sex differences in responses to homeostatic threat and vulnerability to disease. Victor Viau, University of British Columbia. Governed by the hypothalamic-pituitary-adrenal (HPA) neuroendocrine axis, stress-induced elevations in circulating glucocorticoids are adaptive in that they allow the organism to meet the energetic demands of threats to the body. However, chronic or sustained elevations in glucocorticoids are maladaptive and are often associated with mood, metabolic, and cardiovascular disorders. Males and females are differentially predisposed to these disorders, as well as show differences in HPA responses to homeostatic threat. Evidence will be presented to underscore that there is a huge amount of neural substrate dedicated to registering changes in sex steroid hormone status to the paraventricular nucleus of the hypothalamus, the final common pathway regulating adaptive neuroendocrine responses. Stressful experiences and alterations in the serotoninergic (5-HT) neurotransmitter system are implicated as factors contributing to such mood disorders as depression. The 5-HT 1A receptor subtype is not only tied to the stimulatory effects of serotonin on the HPA axis, but also plays a pivotal role in the mechanism of action of antidepressants. The majority of basic and clinical studies on 5-HT, however, have been conducted in male subjects only. Thus, most of what we think we understand about stress, 5-HT and depression may not be the same between males and females. Pathways and mechanisms by which variations in stress HPA axis function may be explained by sex differences in 5-HT 1A receptor activity will also be discussed.

10:30-11:30 **Bench-to-Bedside Lecture.** Coming to Our Senses: Implications of Embodiment for the Pathogenesis and Treatment of Major Depression. C. L. Raison

Coming to Our Senses: Implications of Embodiment for the Pathogenesis and Treatment of Major Depression. CL Raison, Department of Psychiatry, College of Medicine and College of Agriculture and Life Sciences, University of Arizona, Tucson, AZ. Despite ongoing scientific advances in our understanding of brain-body processes central to mental illness, the treatment of the most common of these ailments—major depression—remains little changed over the last 20 years. Indeed, while often effective over the short term, current treatment strategies leave many patients with residual symptoms that predict both chronic disease and treatment resistance. Moreover, increasing data suggest that antidepressants may make the brain more vulnerable to depressive relapse over time. This lecture tackles these limitations by exploring whether better understandings of what causes depression, based on evolutionary science, might provide untapped therapeutic resources. Two key ideas that will emerge from this lecture are that evolutionary processes have "wired" the brain and body together in ways that make it possible to treat depression by affecting the body, rather than the brain directly and that depression evolved in the context of dynamic interactions with others in the environment, especially microbial agents that have powerfully driven human evolution. To demonstrate these ideas, the speaker will provide examples from his own research into treating depression by impacting the body's immune system and by using hyperthermia to specifically alter brain function in ways that relieve depressive symptoms. The talk will conclude with a discussion of theoretical and applied findings suggesting that altering our "conversation" with microbial elements in the internal and external environment might open new vistas for both preventing and treating mental disorders.

3:30-5:30 **Symposia: The role of CRF and CRF receptor expression in the progression and pathology of major depressive disorder.** Chairs: Marion Rivalan and R. Parrish Waters, Cliff Summers

Sex differences in Corticotropin Releasing Factor 1 Receptors: From Molecules to Mood. Bangasser, D. Department of Psychology and Neuroscience Program, Temple University. Stress-related psychiatric disorders, such as anxiety and depression, occur twice as frequently in women as in men. However, the neurobiological

basis for this disparity remains largely unknown. Corticotropin-releasing factor (CRF) orchestrates the stress response and is hypersecreted in stress-related psychiatric disorders. Thus, sex differences in CRF sensitivity could contribute to the sex bias in these diseases. Supporting this idea, neurons in the locus coeruleus (LC) arousal center are more sensitive to CRF in female than male rats. This effect is linked to sex differences in CRF 1 receptor signaling and trafficking. Specifically, the CRF 1 receptor couples more to the Gs protein in female than in male rats, an effect that can account for elevated responses to acute stress. Additionally, stressor exposure in rats and CRF overexpression in mice cause CRF 1 receptor internalization in males only, suggesting that females lack this important cellular adaptation. This sex difference was associated with increased LC neuronal firing in female, but not male CRF overexpressing mice. These studies reveal sex differences at the level of the CRF 1 receptor and suggest that this receptor may be an important pharmaceutical target for treating stress-related disorders in women. Sex differences in CRF 1 receptor function are now being linked to sex differences in anxiety-related behavior. Preliminary data demonstrate that high doses of CRF administered centrally evoke certain anxiety-related behaviors more in female than male rats. These results support the idea that sex differences in CRF sensitivity contribute to sex differences in anxiety behavior, and they indicate that the CRF-evoked behavior procedure may be a useful preclinical model for testing anxiolytic compounds in females. Collectively, these studies highlight that sex difference in CRF 1 receptor function may be an important determinant of female vulnerability to stress-related psychiatric disorders.

The role of CRF in mediating an individual's risk to social stress-induced psychopathology. Susan K. Wood (1,2), Rita J. Valentino (2) 1-Department of Pharmacology, Physiology & Neuroscience, University of South Carolina School of Medicine; 2-Division of Stress Neurobiology, Children's Hospital of Philadelphia. One common stressor encountered by humans is social stress and this has been linked to psychiatric disorders including depression and anxiety. A critical determinant of vulnerability to stress-related pathologies is the individual's coping strategy adopted during stress. Using a social stressor in rats we previously identified two phenotypic responses to social stress. One population is characterized by passive coping behaviors, anhedonia, an endocrine profile similar to melancholic depression in humans, and an exaggerated decrease in heart rate variability, indicating increased cardiovascular disease risk. The other phenotype is characterized by proactive behaviors and exhibits resistance to many of the consequences associated with the passive phenotype. As corticotropin-releasing factor (CRF) is the hallmark of the stress response, we have conducted several studies aimed at elucidating its role in stress susceptibility. As dorsal raphe (DR)-5-HT neurons have been implicated in stress-related psychiatric disorders and are regulated by the stress neuropeptide, CRF, their activity and responses to CRF were compared in social stress and control rats. CRF (30 ng, intra-DR) decreased the discharge rate of 5-HT neurons in control and SL rats. In contrast, CRF activated 5-HT neurons of LL rats. Because inhibition and activation of DR-5HT neurons has been linked to CRF1 and CRF2 receptors, respectively the effects of the CRF2 antagonist, antisauvagine-30 (ASV) were examined. ASV (300 ng, i.c.v.) prevented the CRF-induced activation of DR-5-HT neurons in LL rats. Consistent with the emergence of this CRF2 mediated excitatory response, immunoelectron microscopic studies revealed that social stress resulted in recruitment of CRF2 to the plasma membrane of DR neurons selectively in active coping rats, while the predominant receptor subtype in passive coping rats was CRF1. As such, we evaluated the effects of a CRF1 receptor antagonist, NBI-30775 (10mg/kg/day), on the behavioral response to and consequences of social stress. Interestingly, treatment with a CRF1 receptor antagonist shifted the behavioral phenotype towards an active coping response and inhibited the emergence of behavioral despair, anhedonia, elevated blood pressure, and adrenal hypertrophy. Together, these data suggest that differences in CRF receptor activity may underlie phenotypic differences in responses to and consequences of social stress.

Dissecting CRH-controlled Neurocircuitries of Stress and Anxiety. Nina Dedic, Claudia Kühne, Karina Gomes, Marcel Schieven, Jakob Hartmann, Klaus V. Wagner, Carsten Wotjak, Damian Refojo, Mathias V. Schmidt, Wolfgang Wurst, Jan M. Deussing Max Planck Institute of Psychiatry, Nina Dedic, Claudia Kühne, Karina Gomes, Marcel Schieven, Jakob Hartmann, Klaus V. Wagner, Carsten Wotjak, Damian Refojo, Mathias

V. Schmidt, Wolfgang Wurst, Jan M. Deussing Max Planck Institute of Psychiatry, Department of Stress Neurobiology and Neurogenetics, Munich, Germany. The corticotropin-releasing hormone (CRH) and its high-affinity type 1 receptor (CRHR1) critically control behavioural adaptations to stress and are causally linked to stress-related disorders such as anxiety and depression. So far little was known about the brain regions and specific CRH/CRHR1-controlled neurotransmitter circuits which modulate such behavioural alterations. In this regard, we were recently able to provide a clearer understanding of the interaction of CRH with other neurotransmitter systems by unravelling the identity of anxiety-modulating CRHR1-positive glutamatergic and dopaminergic neurons. Our results provide substantial evidence that anxiety-related behaviour is generated by an imbalance between CRHR1-controlled anxiogenic glutamatergic and anxiolytic dopaminergic systems (Refojo et al., 2011). However, the identity of CRH-releasing neurons and sites of CRH action have not been fully established yet. To specifically address the in vivo function of the neuropeptide CRH we applied conditional mutagenesis to generate respective gain- and loss-of-function mouse models. Mice overexpressing CRH or lacking endogenous CRH in a spatially and temporally controlled fashion allowed investigating the role of CRH in the control of basal emotionality and hypothalamic-pituitary-adrenal (HPA)-axis but also in response to stress. The neurotransmitter type-specific manipulation of CRH on the circuit level further substantiates the diverging roles of CRH during basal and stress conditions, and clearly underlines the ability of the CRH/CRHR1 system to modulate anxiety-related behaviour in opposite directions. Refojo et al. Science 2011, 333:1903-7

Clinical biomarkers for central CRF overexpression – Identifying the right patient for CRF1 antagonistic treatment. Marcus Ising, Florian Holsboer; Max Planck Institute of Psychiatry, Munich, Germany. Depression can be regarded as typical example for a stress-related disorder of the brain. Severe early life stress increases the risk of adult depression and certain stressors trigger the incidence of a depressive episode. Furthermore, a number of patients with acute depression, albeit not all, show an impaired stress hormone regulation, which normalize under a successful antidepressant therapy. Preclinical studies point to a prominent role of CRF in this context, which mainly acts on stress response regulation via CRF receptor 1 (CRF1). Accordingly, a number of CRF1 antagonists have been developed as potential antidepressant and anxiolytic treatments and tested in clinical trials. However, no compound has yet been approved. The most probable reason for this failure is – besides potential pharmacokinetic issues - the unavailability of appropriate biomarkers for central CRF overexpression to select the right patients who should benefit most from CRF1 antagonistic treatment. Overexpression of hypothalamic neuropeptides including CRF seems to be a major factor contributing to an impaired stress response regulation in depression. Another core feature of depression physiology is disinhibited REM sleep connected to elevated cholinergic activity in pons and midbrain, which in turn interacts with central CRF expression. Studies in CRF overexpressing mice suggest a strong link between CRF and disinhibited REM sleep. When re-analyzing the results of a clinical trial with the CRF1 antagonist R121919 in patients with major depression, we could confirm that the best outcome was obtained in patients showing disinhibited REM sleep at baseline before treatment was initiated. Neuropeptide receptor ligands like CRF1 antagonists are highly selective treatments that require the availability of biomarkers identifying the right patients who will optimally benefit from such specific intervention. Our findings suggest that besides measures of stress response regulation, REM sleep disinhibition is a promising candidate for such a biomarker reflecting central CRF overexpression. Such biomarkers might be suitable to identify the right patient for future clinical trials with CRF1 antagonists.

3:30-5:30 **Oral Session 1: Addiction**

The galanin-3 receptor (GALR3) antagonist, SNAP 37889, reduces ethanol consumption in alcohol-preferring mice. Scheller K.J. Department of Human Biosciences, La Trobe University, Bundoora, Victoria, Australia; Ash B.L. Department of Human Biosciences, La Trobe University, Bundoora, Victoria, Australia; Quach T. Bio21 Molecular Science and Biotechnology Institute, Parkville, Victoria, Australia; Williams S.J.

Bio21 Molecular Science and Biotechnology Institute, Parkville, Victoria, Australia; Lawrence A.J. Florey Institute of Neuroscience & Mental Health, University of Melbourne, Parkville, Victoria, Australia; Djouma E. Department of Human Biosciences, La Trobe University, Bundoora, Victoria, Australia. The neuropeptide galanin is implicated in the regulation of emotional states. We have previously shown that the galanin-3 receptor (GALR3) antagonist, SNAP 37889 (30mg/kg), significantly reduces ethanol consumption. The aim of this study was to further characterise the role of the GALR3 in a number of behavioural paradigms to help evaluate the drug's overall efficacy as a potential therapeutic treatment for alcohol abuse. C57BL/6J mice (n=8-12/group) were employed for all experiments. SNAP 37889 (30mg/kg) and vehicle [30% Solutol® HS 15 in 70% phosphate buffer (0.01M, pH=7.4), 1ml/kg] were administered via intraperitoneal injection 30 or 60 mins prior to behavioural testing depending on the length of the test. Locomotor activity/rotarod: There were no significant differences found between SNAP 37889 or vehicle treated mice during the 1hr session for all locomotor parameters explored which suggests the drug does not cause sedation. The time or latency that it took the mice to fall off an accelerated rotarod revealed no significant differences in ataxia. Y-maze: A one-way ANOVA revealed that SNAP 37889 treated mice spent significantly more time in the novel arm, compared to the familiar arm ($p=0.0017$) while both drug groups spent a similar time in the home arm. Furthermore, SNAP 37889 treated mice spent significantly less time in the familiar arm, compared to the vehicle mice ($p=0.0007$). Light/dark test: SNAP 37889 treated mice spent significantly more time (~10 seconds) in the light during their first visit ($p=0.0047$) which may represent a mild anxiolytic effect. Conditioned place preference paradigm: A paired t-test revealed no significant difference in the percentage of time spent in the SNAP 37889 paired zone suggesting that SNAP 37889 is not intrinsically rewarding. Sucrose, Saccharin and ethanol trial: SNAP 37889 significantly reduced consumption of 10% ethanol, 5% sucrose and 0.1% saccharin solutions ($p<0.01$) suggesting that SNAP 37889 reduces the drive to seek out reinforcers, independent of their caloric value. Liver assays: No difference was found in endogenous liver enzyme activity between vehicle and drug mice suggesting that SNAP 37889 must be working centrally. Collectively, this data suggests that antagonism of GALR3 may significantly reduce alcohol intake by decreasing anxiety levels, independent of sedation or a place preference for SNAP 37889. This research highlights a possible therapeutic target, the GALR3, in the treatment of alcoholism.

Strain Dependent Cell Death Induced by Embryonic Alcohol Exposure in Zebrafish. Mahabir, S. Department of Cell and Systems Biology, University of Toronto, Toronto, ON, CA; Chatterjee, D. Department of Psychology, University of Toronto Mississauga, Mississauga, ON, CA; Gerlai, R. Department of Cell and Systems Biology, Department of Psychology, University of Toronto Mississauga, Mississauga, ON, CA. Exposure to alcohol during development can result in a range of abnormalities in the central nervous system from severe to mild depending on the dose. The biological mechanisms that are affected by embryonic alcohol exposure and the genes that influence alcohol effects on development of the brain have not yet been well studied. Studies have shown that low concentrations of alcohol employed for a short period of time during early development of zebrafish causes a disruption in shoaling behaviour. This change in shoaling behaviour is also accompanied by a reduction in the dopaminergic and serotoninergic system and is shown to be strain dependent. One potential underlying mechanism that may account for these changes is programmed cell death or apoptosis. High doses of alcohol have been demonstrated to disrupt signalling pathways such as programmed cell death but these doses are clinically less relevant. In our study, we analyze the effect of low embryonic alcohol exposure on apoptosis in three zebrafish strains (AB, TU, and TL). The level of alcohol exposure we employ is more realistic from the perspective of fetal alcohol spectrum disorders (FASD). We exposed the zebrafish embryo to alcohol at 24 hours post-fertilization (hpf) for 2 hours using two external bath concentrations, 0.00% or 1.00% (EtOH vol/vol%). At 26 hours post-alcohol exposure we analyzed apoptosis in zebrafish embryos using the in situ Cell Death Detection Kit (TMR red). Stained cells were examined with a confocal microscopy employing Zeiss LSM confocal software to collect the images. The number of apoptotic cells in the head regions of each embryo was analyzed using Image ProPlus 6.0 and differences between treatment groups were quantified. We are now completing the data analyses and will report on strain differences in apoptotic cell death

induced by embryonic alcohol exposure in the zebrafish brain: our preliminary results indicate that AB fish exhibit an increase in the number of apoptotic cells when treated with 1.00% but fish of the TU strain appears protected. Genetic variation in individuals may effect how developmental ethanol disrupts signalling pathways. Cell death in the central nervous system may be responsible for neurobehavioural effects associated with FASD in humans. Given the translational relevance of this species, our studies will facilitate the identification of genes and the biochemical mechanisms underlying the effects of embryonic alcohol exposure in humans.

ERK phosphorylation of mGluR5 within the BNST regulates alcohol sensitivity in mice. Rianne R. Campbell, Ryan S. Waltermire, Justin A. Courson, Daniel I. Greentree, Sema G. Quadir, Hadley McGregor, Karen K. Szumlinski; Department of Psychological and Brain Sciences and Neuroscience Research Institute, University of California at Santa Barbara, Santa Barbara, CA, 93106-9660. A history of binge alcohol intake by mice upregulates the activational state of ERK (extracellular signal-regulated kinase) and of PI3K (phosphotidyl inositide-3 kinase) within the bed nucleus of the stria terminalis (BNST). This region is a constituent of the extended amygdala that is highly implicated in mediating both the positive and negative reinforcing properties of alcohol. The present study employed site-directed microinfusions of inhibitors of either ERK (0-100 nM U0126) or PI3K (0-300 nM GDC-0941; 50 nM wortmannin) into the BNST of C57BL/6J (B6) to assay the functional importance of these kinases for alcohol intake under 2-hr Drinking-in-the-Dark (DID) procedures. Interestingly, neither GDC-0941 nor wortmannin infusions affected alcohol drinking during the 2-hr sessions, suggesting that PI3K activity within the BNST is not necessary for heavy drinking. However, to our surprise, intra-BNST infusions of U0125 dose-dependently augmented alcohol intake under DID procedures, suggesting that ERK activity within this region normally curbs excessive alcohol intake. ERK is reported to phosphorylate the mGluR5 receptor at T1123 and S1126, which induces a conformational change in the receptor to facilitate NMDA receptor conductance. Thus, we next assayed the alcohol drinking phenotype of mice with alanine (A) substitutions on these amino acid residues and assayed for the efficacy of intra-BNST infusions of U0126 in these transgenic (TG) mice. TG mice also exhibited greater sensitivity to alcohol when assessed using place-condtioning and rotorod procedures. Moreover, the dose-response function for alcohol intake under continuous free-access and operant conditions was shifted upwards in TG mice and these mice also exhibited sporadically higher alcohol intake under DID procedures. However, when infused with 100 nM U0126, TG mice failed to exhibit a rise in alcohol intake under our 2-hr DID procedure, while this dose of the ERK inhibitor elevated drinking in WT mice. Taken together, these data point to an alcohol-induced increase in ERK activity and ERK-mediated phosphorylation of mGluR5 within the BNST as inhibitory upon behavioral sensitivity to alcohol of relevance to alcoholism-related behaviors. Funding provided by: NIAAA grant AA016650 to KKS

Methamphetamine exposure combined with HIV-1 disease or gp120 expression: Comparison of learning and executive functions in humans and mice. Kesby, J.; Heaton, R.; Young, J.; Umlauf, A.; Woods, S.; Letendre, S.; Markou, A.; Grant, I.; Semenova, S. Department of Psychiatry, University of California San Diego, La Jolla, CA, United States. Methamphetamine (METH) dependence is common among HIV-infected subjects and may exacerbate HIV-associated neurocognitive deficits. The present work evaluated the separate and combined effects of HIV disease and METH on learning and executive functions in humans. Animal models of neuroAIDS suggest that the gp120 protein may induce cognitive deficits, but little is known about the direct translational value of such models. Thus, we also evaluated the separate and combined effects of gp120 expression in the brain and METH exposure on similar cognitive functions in transgenic mice. Human subjects were grouped by HIV serostatus (HIV+ or HIV-) and lifetime METH dependence (METH+ or METH-). Subjects completed a neurocognitive test battery including assessments in the domains of learning and executive functions. Mice (gp120+ and gp120-) were either exposed to an escalating METH binge (METH+) or not (METH-) and were then tested in the attentional set-shifting task (ASST) to assess discrimination learning and executive function. In human subjects, HIV was associated with impairments in learning ($p<0.01$, $d=0.50$), but not in executive function. METH dependence had no significant effect on either domain. However, there

was a significant difference between groups in the frequency of learning impairments ($p<0.05$), with the greatest frequency of impairment observed in the HIV+/METH+ group. In mice, gp120 expression led to a significant impairment in learning ($p<0.05$, $d=0.34$), but not reversal learning. METH exposure had no significant effect on either measure. However, there was a significant difference between groups in the number of mice that failed to complete the ASST ($p<0.05$), with the greatest failure rate observed in the gp120+/METH+ group. These results demonstrate that learning may be sensitive to injury induced by HIV disease in humans and gp120 expression in mice. METH exposure in both humans and mice increased the frequency of learning impairments induced by HIV or gp120 suggesting that specific HIV-associated cognitive deficits may be exacerbated by METH. In addition, our inter-species comparative analyses showed a similar pattern of results suggesting that learning deficits in HIV-infected humans may be partially attributed to the gp120 protein. Thus, gp120-expressing mice represent a viable animal model of neuroAIDS for investigation of the neurobiological mechanisms underlying HIV-associated neurocognitive disorders and its comorbidities (e.g., METH).

Sprague Dawley rats show a behavioral predisposition for ethanol consumption or aversion that can be modulated by serotonin. Rani K. Vasudeva; Lynn G. Kirby; (for both authors) Temple University School of Medicine, Center for Substance Abuse Research, 3500 North Broad St., Philadelphia, PA 19148 USA. Alcoholism afflicts 1 in 13 US adults, and co-morbidity with depression is common. Levels of serotonin (5HT) metabolites in alcoholic or depressed humans and rat strains are lower compared to healthy counterparts. While strains of rats bred for ethanol (EtOH) preference are more commonly used in studies examining the addictive properties of EtOH, we wanted to demonstrate that the out-bred Sprague-Dawley (SD) rat will drink to stable levels and that pharmacological depletion of 5HT will result in an increase in EtOH consumption, thus establishing a link between EtOH intake and 5HT in this strain. Male Sprague Dawley (150 – 200g) rats were placed on the 20% EtOH intermittent access drinking paradigm (IA) to assess voluntary EtOH consumption. At week 3-4, enrichment (a hollow tube) was removed from the cages. Following 8 weeks of IA, one group (n=8) received 3-150mg/kg i.p. injections of the systemic tryptophan hydroxylase inhibitor para-chlorophenylalanine (pCPA) over 3 days and EtOH consumption was measured for additional 4 weeks in IA. A second group (n=32) received i.c.v. injections of 150ug 5,7-dihydroxytryptamine (5,7-DHT), a CNS serotonergic neurotoxin, or vehicle, and was placed back on IA for an additional 4 weeks. During acquisition, rats showed a natural inclination (n=20) or aversion (n=10) for EtOH. In addition, EtOH consumption began or increased significantly following the removal of environmental enrichment. EtOH-drinking rats consumed EtOH to stable baseline levels of 2.4 ± .09 g EtOH/kg/24h. Systemic depletion of 5HT levels with pCPA significantly increased EtOH intake in preferring rats compared to baseline at 3-4 weeks post injections ($p<.05$). Administration of 5,7-DHT also resulted in a significant increase in EtOH consumption compared to baseline 3-4 weeks post depletion ($p<.05$) in EtOH-drinking rats. No effect of 5,7-DHT was seen in the EtOH consumption of EtOH-abstaining rats. Our findings indicate that the SD rat will voluntarily consume EtOH to stable baseline levels that increase with depletion of systemic or CNS 5HT. We also demonstrate that SD rats show a natural inclination or aversion for EtOH, much like the human population. Lastly, our findings support the theory that environmental enrichment may provide protection against the development of drug addiction.

Effects of neonatal maternal separation on behavioral and neural responses to methamphetamine. Pritchard, L. M. UNLV; Hensleigh, E. UNLV; Pierce, M. UNLV; AbuAli, K. UNLV; Lynch, S. UNLV; Fowler, A. UNLV; Egan, J. UNLV; Eby, M. UNLV; Orlewicz, M. UNLV; Jager, A. UNLV; Semmel, M. UNLV. Clinical research has provided ample evidence that stressful life history is a major risk factor for substance abuse and dependence. In particular, traumatic stress during childhood significantly increases the probability of developing substance use disorders later in life. However, the underlying neural mechanisms have been difficult to elucidate in clinical populations due to a variety of practical and ethical limitations. Neonatal maternal separation in rodents has emerged as a useful model of early life stress and has contributed to our understanding of the neural mechanisms responsible for altered stress reactivity and emotionality in survivors of early trauma.

Multiple studies have demonstrated effects of maternal separation on sensitivity to the behavioral effects of drugs of abuse, particularly for cocaine and alcohol. Methamphetamine (METH), despite its widespread abuse and serious public health threats, remains relatively understudied in the maternal separation model. Here, we present a review of recent studies in our lab demonstrating that repeated maternal separation during the first two weeks of postnatal life produces significant changes in a variety of behavioral and neural responses to METH. In particular, we have demonstrated that maternal separation enhances locomotor and stereotyped responses to acute METH and alters conditioned preference for a METH-paired environment and loss of dopaminergic markers in the striatum after a binge dosing regimen. Furthermore, we have found sex differences in these effects, which have important clinical implications, given the observed gender differences in METH use and dependence in humans. Interestingly, we and others have not observed similar effects of maternal separation on responses to d-amphetamine. Potential reasons for these differential effects will be discussed.

Neuropsychological Influences on Cognitive Training. Sheida Rabipour, University of Ottawa; Patrick Davidson, University of Ottawa. Cognitive training is a promising method to examine neural plasticity and receptiveness to learning, and may diminish the impact of age-related brain and behavioural disorders. Nevertheless, basic questions on the neurological and psychological bases of such training remain. Crucially, few studies address the potential effects of participant expectation on training (e.g., via the placebo effect), despite ample evidence suggesting the importance of such expectation in other contexts. We seek to determine the effects of expectation on cognitive function and psychological wellbeing following cognitive training in adults. Specifically, our study evaluates the influence of receiving a high vs. low expectation message regarding the effectiveness of cognitive training. Using an online survey, we examine the baseline beliefs and malleability of expectations on cognitive training in younger and older adults. We then evaluate participant performance on cognitive and neuropsychological tests before and after administering a weeklong cognitive training program. Our analyses aim to tease apart the effects of expectation from those of computerized cognitive exercise, affording a better scientific understanding of psychological influences on behaviour and cognitive learning. Understanding how participants respond to cognitive training as a function of psychological parameters such as expectation is critical to maximizing the effectiveness of cognitive training and determining its potential as a non-drug alternative to the treatment of age-related diseases such as dementia.

Transcranial infrared laser stimulation of cognitive functions. Francisco Gonzalez-Lima* and Douglas W. Barrett, Department of Psychology and Institute for Neuroscience, University of Texas at Austin, Austin, TX 78712. Low-power near-infrared lasers and LEDs represent a novel non-invasive intervention shown to regulate neuronal function in cell cultures, animal models, and clinical conditions. Near-infrared light stimulates mitochondrial respiration by donating photons to cytochrome oxidase because cytochrome oxidase is the main molecular acceptor of photons from red-to-near-infrared light in neurons. Memory retention has been improved by increasing neuronal mitochondrial respiration with methylene blue, a drug that at low doses donates electrons to the respiratory enzyme cytochrome oxidase. Therefore, interventions that stimulate cytochrome oxidase, such as low-power red-to-near-infrared lasers may also improve cognitive functions. Light that intersects with the absorption spectrum of cytochrome oxidase was given to rats using LEDs, or applied to the forehead of humans with a low-power laser diode that maximizes tissue penetration and has been used safely in humans for other indications. We found that this type of brain stimulation enhanced cortical oxygen consumption (measured in vivo with fluorescence-quenching oxygen probe and near-infrared spectroscopy) and cytochrome oxidase (measured with enzyme spectrophotometry and histochemistry) in both rat and human prefrontal cortex. In rats, red-to-near-infrared light stimulation after fear extinction learning prevented fear renewal as compared to controls. In humans, transcranial infrared laser stimulation to the forehead improved prefrontal cortex-related cognitive functions, such as sustained attention and working memory. A delayed-match-to-sample task showed a significant improvement in laser-stimulated vs. placebo control groups of people as measured by memory retrieval latency and number of correct trials. Together these studies suggest that transcranial brain stimulation with red-to-near-infrared light may be used as a non-invasive and efficacious

approach to increase neuronal mitochondrial respiration functions related to improvement of prefrontal cognitive functions. This fascinating brain stimulation approach may become a new non-invasive, neurocognitive-enhancing intervention in animals and humans.

5:30-7:30 **Poster Session 2**

40. **The role of hippocampal dopamine D1-type receptors in social learning, feeding behavior and social interactions in male and female mice.** Matta, R., Tiessen, A. N., Kivlenieks, M. M., Meersseman, A. M., Adjei-Afriyie, Y. O., & Choleris, E. Department of Psychology and Neuroscience Program, University of Guelph, Guelph, ON N1G 2W1 Canada. The neurotransmitter dopamine is involved in many motivationally relevant behaviors such as drug abuse, feeding behavior and social learning. With systemic studies, our lab has previously found an association between dopamine D1-type receptors and the social learning of food preferences (Choleris et al., 2011), however, the brain regions mediating this effect remain unclear. The ventral tegmental area has dopaminergic projections to many limbic structures, including the hippocampus, a site well known for its role in learning and memory processing, including social learning. We have micro-infused the dopamine D1-type antagonist SCH23390 (at 1, 2, 4 and 6 μg/μL) directly in the Cornu Ammonis 1 (CA1) region of adult male and female CD1 mice 15 minutes before a 30-minute social interaction where mice acquire a food preference from a same-sex conspecific. Consistent with our previous systemic work, we found that the highest dose of SCH23390 blocked social learning in both males and females, without influencing the total amount of food consumed. Furthermore, the impaired social learning was not due to reduced exposure to the socially carried food odor as video analysis of the social interactions revealed no drug effects on oronasal investigation. Moreover, an olfactory discrimination task revealed that animals infused with 6 μg/μL of SCH23390 could discriminate between the food-types used in the social learning test. Hence, blocking hippocampal dopamine D1-type receptors may have influenced social learning specifically. Such results may help our understanding of the role that hippocampal dopamine receptors play in the social brain. Supported by NSERC.

41. **Prenatal methamphetamine affects neurotransmitter levels in adult ventral hippocampus.** Slamberova R. Charles University in Prague, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic; Fujakova M. Prague Psychiatric Center, Department of Biochemistry and Brain Pathophysiology, Prague, Czech Republic, Institute of Chemical Technology, Prague, Czech Republic; Vrajova M. Prague Psychiatric Center, Department of Biochemistry and Brain Pathophysiology, Prague, Czech Republic; Sirova J. Prague Psychiatric Center, Department of Biochemistry and Brain Pathophysiology, Prague, Czech Republic, Institute of Chemical Technology, Prague, Czech Republic; Kacer P. Institute of Chemical Technology, Prague, Czech Republic; Ripova D. Prague Psychiatric Center, Department of Biochemistry and Brain Pathophysiology, Prague, Czech Republic; Horacek J. Prague Psychiatric Center, Department of Biochemistry and Brain Pathophysiology, Prague, Czech Republic, Institute of Chemical Technology, Prague, Czech Republic. An increased abuse of methamphetamine among pregnant women has become a widespread problem. This study shows how prenatal exposure to methamphetamine affects levels of monoaminergic, GABA and glutamate neurotransmitters and their metabolites in ventral hippocampus after a challenge dose of methamphetamine (1 mg/kg i.p.) or saline in adult female offspring. We found that the basal levels of dopamine and its metabolites HVA and 3MT, serotonin and glutamate in prenatally methamphetamine-exposed animals were higher compared to controls. Further, the challenge injection of methamphetamine in adulthood caused saline-exposed animals to have increase in dopamine, 3MT, HVA and serotonin levels when compared to methamphetamine-exposed rats. Thus methamphetamine injection in adult rats exposed to this drug in-utero produces irreversible changes on molecular level. Supported by: GACR P303/10/0580, PRVOUK P34

42. **Abuse liability and toxicity of "bath salts" (i.e. synthetic cathinones) as revealed by Intravenous drug self-administration and ex-vivo MRI.** Watterson L, Department of Psychology, Arizona State University; Olive MF, Department of Psychology, Arizona State University. In the last few years,

designer drugs known as synthetic cathinones have emerged as popular "legal high" replacements of illicit stimulants such as methamphetamine, cocaine, and MDMA (ecstasy). While these drugs have collectively been referred to as "bath salts", they have also been falsely marketed as many other commercial products (e.g. "plant food", "glass cleaner", "iPod cleaner", and "research chemicals") in order to circumvent regulatory controls. Since their appearance on drug markets, these drugs have led to an increasing number of calls to poison control centers as well as numerous reports of toxicity, adverse psychological and behavioral effects, and death. While the rise in synthetic cathinone use is now well documented, little scientific data exists regarding the relative abuse liability of these substances and whether consumption patterns are primarily episodic ("controlled" recreational use) or compulsive (characteristic of addiction). In this presentation, I will first provide a historical overview of synthetic cathinone use followed by a presentation of novel abuse liability data collected in our laboratory using rodent intravenous self-administration and intracranial self-stimulation techniques for the synthetic cathinones MDPV and methylone along with the prototypical psychostimulant methamphetamine. Next, I will present ex vivo MRI data revealing macro-scale changes in brain structures that result from chronic self-administration of MDPV compared to methamphetamine and sucrose controls. I will conclude by discussing these results with an emphasis on informing future synthetic cathinone research, drug policy, and treatment.

43. **Toluene overexpsoure provokes alterations in memory and hippocampal brain structure of adolescent and adult rats.** Mzia Zhvania[1], Nadezhda Japaridze[2], Manana Dashniani[2], Maia Burjanadze[2], Tamar Bikashvili[2], Nino Pochkhidze[1], [1]Ilia State University, Tbilisi, Georgia; [2]I. Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia. The present study has been undertaken to elucidate if toluene over-exposure provokes immediate and persisting effect on learning, memory and hippocampal structure in adolescent and adult rats. We exposed male Wistar rats at ages 28-32 (adolescensts) and 75-80 (adults) to 2000 ppm for 40 days. The immediate and persisting effects (immediately after the end of 40 days toluene exposure and 90-day after toluene exposure, cprrespondingly) on (i) behavior in multi-branch maze, (ii) exploratory behavior and recognition memory in open field and (iii) hippocampal CA1 and CA3 structure were elucidated. The results revealed that toluene chronic exposure affects the structure of the hippocampus, behavior in multi-branch maze, exploratory behavior and recognition memory in adolescent and adult rats. In all cases the effects are age-dependent. In particular, in adolescent rats the more significant behavioral and structural alterations were observed immediately after toluene over-exposure, while in adult rats the most considerable was persisting effect (90 days after withdrawal). Such data indicate that the character of alterations depends upon the postnatal age of testing of the animals. The results are also additional evidence that hippocampus – the neural substrate for learning and memory, may contribute to the pathophysiology of toluene abuse in organisms of different age.

44. **The alterations provoked by toluene over exposure on locomotor activity, behavior in maze and hippocampal structure in adolescent and adult rats.** Mzia Zhvania, Ilia State University, Tbilisi, Georgia. Nadezhda Japaridze, I. Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia. Manana Dashniani, I. Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia. Maia Burjanadze, I. Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia. Tamar Bikashvili, I. Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia. Nino Pochkhidze, Ilia State University, Tbilisi, Georgia. The present study has been undertaken to elucidate if toluene over-exposure provokes immediate and persisting effect on learning, memory and hippocampal structure in adolescent and adult rats. We exposed male Wistar rats at ages 28-32 (adolescensts) and 75-80 (adults) to 2000 ppm for 40 days. The immediate and persisting effects (immediately after the end of 40 days toluene exposure and 90-day after toluene exposure, cprrespondingly) on (i) behavior in multi-branch maze, (ii) exploratory behavior and recognition memory in open field and (iii) hippocampal CA1 and

CA3 structure were elucidated. The results revealed that toluene chronic exposure affects the structure of the hippocampus, behavior in multi-branch maze, exploratory behavior and recognition memory in adolescent and adult rats. In all cases the effects are age-dependent. In particular, in adolescent rats the more significant behavioral and structural alterations were observed immediately after toluene over-exposure, while in adult rats the most considerable was persisting effect (90 days after withdrawal). Such data indicate that the character of alterations depends upon the postnatal age of testing of the animals. The results are also additional evidence that hippocampus – the neural substrate for learning and memory, may contribute to the pathophysiology of toluene abuse in organisms of different age.

45. **Incubation of cocaine-craving relates to a sensitization of cue-mediated glutamate over-flow in the vmPFC.** Christina B. Shin, Michela M. Serchia, John R. Shahin, Anna E. Agaronova, & Karen K. Szumlinski Dept Psychological and Brain Sciences, University of California, Santa Barbara. Relapse to drug-taking is a reoccurring phenomenon impairing addiction recovery that can be triggered by the elicitation of intense drug craving upon re-exposure to drug-paired cues. Cue-elicited drug craving increases in a time-dependent manner during drug abstinence - a phenomenon termed "incubation of craving". The neural substrates of this phenomenon are not fully understood but may involve a sensitization of cue-elicited neurotransmitter release within the ventromedial prefrontal cortex (vmPFC), based on the results of extant neuropharmacological studies. To test this hypothesis, male Sprague-Dawley rats were trained to lever-press for either cocaine (0.25 mg/infusion; 6 h/day) or sucrose pellets (45 mg). In both cases, reinforcer delivery was signaled by a tone-light compound stimulus and the number of reinforcer/cue presentations allowed for sucrose rats was capped at 102, which corresponds to the average number of reinforcers infused by cocaine subjects. After 10 consecutive days of self-administration, animals were left undisturbed for either 3 or 30 days. Then, rats underwent a 3-h in vivo microdialysis session in the operant chamber, during which animals were allowed to respond for presentation of the cues, in the absence of reinforcer delivery. As expected, cocaine animals exhibited a time-dependent intensification of responding on the lever that previously delivered cocaine. Sucrose animals also exhibited sensitized responding, but the behavior was not lever-selective. The opportunity to lever-press for cocaine-paired cues elicited a time-dependent sensitization of vmPFC glutamate release during withdrawal. Interestingly, cue-elicited dopamine release exhibited a tolerance-like effect in the cocaine animals. In contrast, the rise in vmPFC glutamate and dopamine observed during the opportunity to lever-press for sucrose-paired cues did not vary with the passage of time. These data provide novel evidence that the glutamate responsiveness of the vmPFC incubates during protracted withdrawal in parallel with the behavioral responsiveness to cocaine-paired cues. This heightened cortifugal glutamate drive likely contributes to the desensitization of vmPFC mGluR1/5 receptors underpinning extinction learning deficits reported in "incubated" animals and pose pharmacotherapeutic strategies that curb corticofugal glutamate responsiveness to cocaine-paired cues as a viable strategy for facilitating addiction recovery. Funded by NIH grant DA024038.

46. **The role of environmental cues, their effect on navigational tactics, and its application to the natural ecology of Nautilus.** Gregory Jeff Barord (CUNY Graduate Center and Brooklyn College), Rebecca Derman (Brooklyn College), Chengui Ju (CUNY Graduate Center and Brooklyn College), Theresa Vargas (Brooklyn College), Jennifer Basil (CUNY Graduate Center and Brooklyn College. The genera Nautilus and Allonautilus are the remnants of a lineage of cephalopods that appeared in the Cambrian Period (~500 million years ago). Nautiluses retain plesiomorphic features of the ancestral cephalopod line, including neural development, allowing us to examine evolutionary and ecological pressures contributing to behavioral and neural complexity in modern cephalopods. The genus Nautilus includes several different species that inhabit complex coral-reef slopes in the Indo-Pacific and make daily migrations from cold, deep waters (500m) to warmer, shallow waters (75m) at night. Using spatial cues during these migrations may be adaptive for hunting and predator avoidance behaviors. Here we

focus on what type of environmental cues may inform Nautilus, the content and mechanisms of their spatial learning and memory, and how pressures in their natural habitat may relate. We tested nautiluses in laboratory trials using an inverted Morris water maze to address three specific aims: 1) habituation, 2) spatial exploration and latent learning, and 3) navigational tactics. While our results continue to support previous work that Nautilus can learn environmental cues in the absence of rewards, our data also indicates that the navigational tactics of Nautilus shift depending on the presence and location of beacon. This work continues to show that nautiluses are capable of complex behaviors, similar to coleoid cephalopods, despite marked differences in their neural complexity. Perhaps these abilities are conserved in homologous structures in the simpler brain of Nautilus, or ecological pressures of their habitat have led to analogous abilities despite their neural differences. Determining the mechanisms of behavioral complexity in plesiomorphic nautiluses is crucial to understanding evolutionary pressures shaping neural and behavioral complexity in a lineage with a heavy investment in brains.

47. **Permanent depletion of serotonin increases risky decision-making and impairs acquisition of the rat gambling task.** Authors: F.D. Zeeb(1), C.A. Winstanley(2), P.J. Fletcher(1,3,4) Affiliations: 1. Centre for Addiction and Mental Health, Section of Biopsychology, Toronto ON, Canada. 2. University of British Columbia, Psychology Department, Vancouver BC, Canada. 3. University of Toronto, Department of Psychiatry, Toronto ON, Canada. 4. University of Toronto, Department of Psychology, Toronto ON, Canada. Human and animal research strongly implicates serotonin (5-hydroxytryptamine, 5-HT) in decision-making and altered functioning of the 5-HT system may disrupt the ability to learn from loss or punishment. We used the rat gambling task (rGT), a rodent analogue of the Iowa Gambling Task (IGT), to test the hypothesis that 5-HT contributes to decision-making by modulating the significance of punishment-related signals. Male Long Evans rats received a sham surgery or a permanent 5-HT depletion accomplished by an intracerebroventricular infusion of 5,7-dihydroxytryptamine (5,7-DHT), which depleted 5-HT in the forebrain by 75-85%, either before or after rGT training. The rGT took place in 5-hole operant chambers in daily 30min sessions, during which rats chose among four options. Each option differed in reward size (sucrose pellets), frequency of reward delivery, and duration of a timeout period during which rats were not rewarded and initiation of the next trial was halted until the end of the punishment. Therefore—similar to losing on the IGT—timeouts result in less reward earned per unit time. In both the rGT and IGT the optimal strategy is to choose preferentially from advantageous options that yield smaller immediate gains but less loss and therefore greater long-term reward. Depleting 5-HT did not alter choice preference compared to sham-control rats when the lesion occurred after rGT training. In contrast, rats that received a pre-training 5,7-DHT lesion demonstrated a marked impairment in task acquisition and performance. These rats were slower to learn the optimal strategy and chose the disadvantageous, risky options—associated with greater loss—more often than controls. Additionally, in sham-control rats, amphetamine increased choice of the option leading to less loss whereas an injection of the 5-HT1A receptor agonist 8-OH-DPAT moderately decreased choice of the disadvantageous options; both effects were blocked in 5-HT depleted rats. In conclusion, long-term depletion of 5-HT may impair decision-making by dampening the significance of loss, biasing animals to choose disadvantageously despite the negative consequences associated with these options. As impairments in decision-making processes are observed in a wide range of psychiatric disorders, including depression, pathological gambling, and substance abuse, these results may provide insight into the potential role of 5-HT in decision-making in such populations where the 5-HT system may be compromised

48. **Nucleus accumbens glutamate bidirectionally regulates methamphetamine addiction vulnerability.** Lisa M. Schwartz (1), Kevin D. Lominac (1), Melissa G. Wroten (1), Paige N. Ruiz (1), Bailey W. Miller (1), Jonathan Holloway (1), Katherine O. Travis (1), Ganesh Rajasekar (1), Dan Maliniak (1), Andrew B. Thompson (1), Lawrence E. Urman (1), Hanna Barrett (1), Tamara J. Phillips (2), Karen K.

Szumlinski (1); (1) Department of Psychological and Brain Sciences and the Neuroscience Research Institute, University of California at Santa Barbara, Santa Barbara, CA, 93106-9660, USA; (2) Behavioral Neuroscience and Methamphetamine Abuse Research Center, Oregon Health & Science University; Veterans Affairs Medical Center, Portland, OR, 97239, USA. Genetic factors are considered significant contributors to individual differences in psychomotor stimulant addiction vulnerability, and perhaps addiction severity. Addiction severity, in particular drug-seeking behavior, is associated with anomalies in glutamatergic neurotransmission within the nucleus accumbens (NAC). Previous studies of MA-injected mice identified elevated basal extracellular glutamate levels, a sensitized glutamate response to a MA challenge injection and elevated expression of the Homer2 versus Homer1 isoforms of glutamate receptor scaffolding proteins within the NAC as consequences of subchronic treatment with subtoxic MA (10 X 2 mg/kg). Herein, we employed a multi-faceted approach to probe the relation between methamphetamine (MA) preference and elevated indices of NAC glutamate transmission. In one study, we infused intra-NAC the non-selective excitatory amino acid transporter inhibitor TBOA and the mGluR2/3 autoreceptor agonist APDC to raise and lower, respectively, NAC glutamate prior to a test for a MA-conditioned place-preference (elicited by 4 X 2 mg/kg MA) in C57BL/6J (B6) mice. TBOA infusion facilitated, while APDC infusion prevented, the expression of a MA place-preference. In a 2nd study, we employed immunoblotting and in vivo microdialysis procedures to compare mice from lines selectively bred for high versus low MA drinking (respectively, MAHDR and MALDR) and identified several neurochemical abnormalities within the NAC of MA-naïve MAHDR mice that resembled those observed in MA-sensitized animals including: elevated basal glutamate content, a "pre-sensitized" rise in extracellular glutamate upon acute MA injection, elevated Homer2 versus Homer1 expression. In a 3rd study, we employed immunoblotting to compare protein expression between B6 mice that expressed place-preference, place-aversion or no change in behavior following our MA-place-conditioning regimen. Compared to saline-conditioned controls, only B6 mice exhibiting place-preference exhibited elevated Homer2 versus Homer1 expression in the NAC and this co-occurred with increased indices of ERK activity. Together, these data point to an idiopathic or a MA-induced hyper-glutamatergic state within the NAC as important for the manifestation of MA reward, which has implications for both early intervention and prevention of MA addiction and related neuropsychiatric disorders.

49. **Zebrafish and conditioned place preference: a translational model of drug addiction.** Collier, A. The University of Southern Mississippi; Khan, K. The University of Southern Mississippi; Caramillo, E. The University of Southern Mississippi; Echevarria, D. 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. Efficacious treatments remain few in number, the development of which will be facilitated by comprehension of environmental, genetic, pharmacological and neurobiological mechanisms implicated in the pathogenesis of addiction. 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., drug abuse). Behavioral quantification within the conditioned place preference (CPP) paradigm serves as a measure of the rewarding qualities of a given substance. If the animal develops an increase in preference for the drug paired environment, it is inferred that the drug has positive-reinforcing properties. Here we present the utility of the zebrafish model and report CPP behavior following a single exposure to alcohol and caffeine.

50. **Enhanced fear conditioning in mice exposed to perinatal ketamine.** Khan, A. Department of Psychiatry, UCSD, 9500 Gilman Dr., La Jolla, CA 92093-0804; Behrens, M. Salk Institute for Biological Studies ,10010 North Torrey Pines Road, La Jolla, CA 92037; Risbrough, B. Department of Psychiatry, UCSD, 9500 Gilman Dr., La Jolla, CA 92093-0804, Research Service, VA San Diego

Healthcare System, 3350 La Jolla Village Drive, San Diego, CA, 92037; Powell, S. Department of Psychiatry, UCSD, 9500 Gilman Dr., La Jolla, CA 92093-0804, Research Service, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA, 92037. Alterations in inhibitory GABAergic neurons are implicated in different psychiatric disorders such as autism and schizophrenia. Human studies have shown that patients with schizophrenia have reduced functioning of GABAergic interneurons in the brain, particularly prefrontal cortex and hippocampus. Animal studies have also shown that alteration in GABA function leads to behavioral phenotypes that resemble the core domains affected in schizophrenia. In the current study we tested the effects of perinatal ketamine on behaviors relevant to neuropsychiatric disorders. Previously we have shown that the repeated administration of ketamine during the second postnatal week decreased parvalbumin immunoreactivity in GABAergic interneurons in the prelimbic region of medial prefrontal cortex. This loss of PV in the prelimbic cortex was associated with disinhibition of pyramidal neurons. We hypothesized that administration of ketamine during early development (perinatal administration), which leads to decreased inhibitory tone in prefrontal cortex, will produce enduring behavioral deficits in mice. C57BL/6 mice were injected with 30 mg/kg (s.c) ketamine or saline on postnatal days 7, 9 and 11. Mice were then tested in prepulse inhibition of startle and fear conditioning tests. Mice exposed to perinatal ketamine showed a trend for increased prepulse inhibition. In the fear conditioning test, mice exposed to perinatal ketamine showed enhanced contextual and cued fear conditioning ($p<0.05$) compared to saline-injected mice. These data indicate that the loss of PV interneurons associated with perinatal ketamine administration leads to disinhibition of prefrontal cortex and enhanced fear expression in mice.

51. **Phosphodiesterase 1B knockout mice are resistant to the induction of depression-like behavior.** J. R. Hufgard, M. R. Skelton, M. T. Williams, C. V. Vorhees (Cincinnati Children's Hospital Medical Center). Phosphodiesterases (PDE) are regulators of the second messengers, cAMP and cGMP, that have been implicated in disorders such as depression and schizophrenia. The PDE superfamily consists of 11 families each with multiple isoforms. PDE4 inhibitors are effective antidepressants but have unwanted side effects that prevent them from being clinically useful. Little is known about the role of other PDE families in neuropsychiatric disorders. PDE1b is expressed in the striatum, hippocampus, and amygdala; regions implicated in psychiatric diseases. We developed a constitutive Pde1b knockout (KO) mouse and backcrossed it to C57BL6 mice for >7 generations. To determine its role in depression we tested KO and wildtype (WT) littermates from het x het crosses with no more than one offspring per genotype per litter on the forced-swim (FST) and tail-suspension tests (TST). The TST showed that KO mice are resistant to the induction of immobility and in the FST KO mice showed a significant reduction in total immobility compared with WT littermates. In another experiment we compared KO and WT mice treated with 20 mg/kg of fluoxetine or saline given 23.5, 5, and 1 h prior to the FST. The data reaffirmed that in saline-treated groups KO mice have reduced immobility compared with WT mice. WT mice treated with fluoxetine had a similar phenotype as the KO mice of decreased immobility compared with WT-saline animals. In addition, KO mice treated with fluoxetine showed increased immobility compared with all other groups. We next compared KO and WT mice treated with 20 mg/kg of bupropion or saline given 30 min prior to the FST. Bupropion reduced the immobility time of the WT mice compared with saline controls. KO mice treated with bupropion had immobility times that were decreased compared with all other groups. The results show that Pde1b KO mice are resistant to the induction of depression-like behavior. They also are affected by the SSRI fluoxetine and the non-SSRI bupropion, demonstrating that Pde1b is involved in depression-related behavior independent of the action of reuptake inhibitors. Pde1b KO mice may be a useful model for elucidating downstream postsynaptic targets for the treatment of depression.

52. **Cacna1c haploinsufficiency leads to altered mesolimbic dopamine system function.** Terrillion, C. Department of Psychiatry and Program in Neuroscience; Arad, M. Department of Psychiatry; Dao, D.

Department of Psychiatry; Cachope, R. Department of Anatomy and Neurobiology; Cheer, J. Department of Psychiatry, Department of Anatomy and Neurobiology, and Progra in Neuroscience; Gould, T. Department of Psychiatry, Department of Anatomy and Neurobiology, Department of Pharmacology, and Program in Neuroscience. Background: 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 decreased 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) and wild-type (WT) 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), subsecond DA release and reuptake in the nucleus accumbens of HET and WT mice was measured following stimulation of the ventral tegmental area. Recordings were taken at a series of stimulation amplitudes and after GBR12909 administration. Western blot was used to determine levels of dopamine transporter (DAT) protein. Results: HET mice manifested significantly reduced hyperlocomotion following acute administration of psychostimulants specific to DAT (amphetamine, cocaine, and GBR12909) but not to glutamate (MK-801), as well as delayed sensitization. There was no effect of genotype on stereotypic behavior or CPP. FSCV revealed that HET mice had significantly more rapid DA reuptake following 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. FSCV revealed that Cav1.2 has a role in presynaptic ML-DA system function, including a likely role in regulating DAT function. However, this is not due to total levels of DAT protein suggesting that DAT activity is regulated through an alternative mechanism.

53. **Chronic social stress during puberty alters appetitive male sexual behavior and neural metabolic activity.** Bastida, C. University of Texas at Austin; Puga, F. University of Texas at Austin; Gonzalez-Lima, F. University of texas at Austin; Jennings, K. University of Texas at Austin; Wommack, J. University of Texas at Austin; Delville, Y. University of Texas at Austin. Repeated social subjugation in early puberty lowers testosterone levels. We used hamsters to investigate the effects of social subjugation on male sexual behavior and metabolic activity within neural systems controlling social and motivational behaviors. Subjugated animals were exposed daily to aggressive adult males in early puberty for postnatal days 28 to 42, while control animals were placed in empty clean cages. On postnatal day 45, they were tested for male sexual behavior in the presence of receptive female. Alternatively, they were tested for mate choice after placement at the base of a Y-maze containing a sexually receptive female in one tip of the maze and an ovariectomized one on the other. Social subjugation did not affect the capacity to mate with receptive females. Although control animals were fast to approach females and preferred ovariectomized individuals, subjugated animals stayed away from them and showed no preference. Cytochrome oxidase activity was reduced within the preoptic area and ventral tegmental area in subjugated hamsters. In addition, the correlation of metabolic activity of these areas with the bed nucleus of the stria terminalis and anterior parietal cortex changed significantly from positive in controls to negative in subjugated animals. These data show that at mid-puberty, while male hamsters are capable of mating, their appetitive sexual behavior is not fully mature and this aspect of male sexual behavior is responsive to social subjugation. Furthermore, metabolic activity and coordination of activity in brain areas related to sexual behavior and motivation was altered by social subjugation.

54. **Motivation Orientation and Propensity for Flow Among Elite American Football Players**. Damian Vaughn, M.A. (PhD Student) Claremont Graduate University. My presentation will cover findings from a qualitative investigation into the intrinsic motivation orientation (IMO), extrinsic motivation

orientation (EMO), and propensity for flow experiences in American football was conducted in order to gain greater insight into the nature of motivation and flow in sport. Six NFL players and six NCAA Division I football players were interviewed on their motivation orientation to the game of football over the course of their careers and the extent to which they attribute changes in motivation orientation to their ability to achieve flow in competition. While the NFL players expressed a significant increase in EMO from college to the NFL, they also generally reported experiencing a higher frequency of flow than in any other time in their careers. The football players were questioned extensively about the nature and level of IMO and EMO at different levels of competition in order to understand what underlying factors contribute to achieving flow when the increase of external rewards and pressures to perform become more salient at higher levels of competition. Drawing on the experience of elite football players may enhance understanding of motivation and flow as they occur in sport.

55. **The antipsychotic drug haloperidol reduces the efficacy of environmental enrichment after traumatic brain injury.** Jacob B. Leary, Megan J. LaPorte, Elizabeth A. Ogunsanya, Anna M. Greene, Kristin E. Free, Jeffrey P. Cheng, Corina O. Bondi, and Anthony E. Kline. Physical Medicine and Rehabilitation, Safar Center for Resuscitation Research, Center for Neuroscience, Psychology, and Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA. Antipsychotic drugs (APDs) are routinely provided to alleviate clinical traumatic brain injury (TBI)-induced agitation. Previous studies from our laboratory have shown that chronic administration of haloperidol (HAL) impedes the acquisition of spatial learning in a water maze task. Conversely, environmental enrichment (EE) has consistently been shown to facilitate recovery after TBI. Given that APDs are likely to be provided chronically during rehabilitation, we sought to investigate the combined effect of HAL and EE (i.e., preclinical rehabilitation) on behavioral outcome after TBI. It was hypothesized that EE would reduce the deleterious effect of HAL. Fifty-three isoflurane-anesthetized male rats received a controlled cortical impact (2.8 mm deformation at 4 m/s) or sham injury and then were randomly assigned to four TBI and four sham groups that were further divided into EE and standard (STD) housing. HAL was administered at a dose of 0.5 mg/kg and saline vehicle (VEH) was provided at a volume of 1.0 mL/kg. Treatments began 24 hours after surgery and were administered intraperitoneally once every day for 3 weeks. Function was assessed by established motor (beam) and cognitive (Morris water maze) tests on days 1-5 and 14-19, respectively. No differences were revealed between the sham groups in any assessment and thus the data were pooled. Furthermore, no statistical differences were observed between the TBI + STD + HAL and TBI + STD + VEH groups in either beam walking ($p = 0.68$) or acquisition of spatial learning, although there was a strong trend for HAL to be worse in the maze ($p = 0.067$). The TBI + EE + VEH group was better in motor and cognitive function relative to the TBI + STD + VEH and TBI + STD + HAL groups (p's < 0.0024), but did not differ from the TBI + EE + HAL group ($p = 0.179$ and 0.0459, respectively; $p = 0.005$ required by the Bonferroni/Dunn post-hoc test, which corrects for multiple comparisons). These data demonstrate that EE is beneficial after TBI, which replicates previous studies. The data further show that EE can attenuate the negative effects of HAL on cognition ($p = 0.0007$), but HAL in turn reduces the efficacy of EE as demonstrated by no differences between the TBI + EE + HAL and TBI + STD + VEH groups ($p = 0.10$). Several ongoing studies in our laboratory are investigating this complex interaction between APDs and rehabilitation after TBI.

56. **Environmental enrichment as a preclinical model of neurorehabilitation.** Vincent V. Mattiola, Jacob B. Leary, Anna M. Greene, Jeffrey P. Cheng, Christina M. Monaco, Corina O. Bondi, Anthony E. Kline, Physical Medicine and Rehabilitation, Safar Center for Resuscitation Research, Center for Neuroscience, Psychology, and Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA. Environmental enrichment (EE) consists of increased living space, complex stimuli, and social interaction that promotes exploration and confers improvements in behavioral outcome and histopathology after experimental traumatic brain injury (TBI) vs. standard (STD) housing. However, as

a model of rehabilitation, continuous EE is not clinically relevant due to the timing parameters of the typical EE and thus translatability could be limited. Specifically, TBI patients typically receive rehabilitation only after critical care has been provided and then only for 3-6 hours per day. Thus, to mimic the clinic, the goal of this study was to determine whether delaying EE by three days and providing only six hours per day would provide benefits similar to continuous EE. It was hypothesized that no significant differences would be revealed between the two EE approaches. To address this rehabilitation relevant issue, isoflurane-anesthetized male rats were subjected to a controlled cortical impact (2.8 mm depth at 4 m/s) or sham injury and randomly assigned to TBI+EE (continuous), TBI+EE (3 day delayed, 6 hr day), and respective sham controls. Motor function (beam-balance/beam-walk) was assessed on post-operative days 1-5. Spatial learning/memory (Morris water maze) was evaluated on days 14-19. The data showed that EE, regardless of timing, improved motor and cognitive function compared to STD housing ($p < 0.0001$). Moreover, there were no differences between the TBI+EE (continuous) and TBI+EE (3 day delayed, 6 hr day), $p > 0.05$. These data demonstrate that delayed and abbreviated EE produces motor and cognitive benefits similar to continuous EE after TBI and thus further supports EE as a preclinical model of neurorehabilitation. Ongoing studies are evaluating the effects of longer delays in implementing EE after TBI.

57. **Exploring cognitive function in obesity: assessment of 5-choice serial reaction time task performance in leptin-knockout rats.** Adams, W. UBC Institute of Mental Heath and Department of Psychology; D'souza, A. Department of Cellular & Physiological Sciences; Sussman, J. Department of Psychology; Kieffer, T. Department of Cellular & Physiological Sciences; Winstanley, C. Department of Psychology; all at University of British Columbia, Canada. Background: Evidence suggests that impulse control deficits may contribute to excessive food intake in some individuals with obesity. In addition to its known role in regulating appetite and energy expenditure, the adipocyte hormone, leptin, also directly modulates the activity of central dopaminergic circuits. While dopamine is involved in mediating impulsivity, the influence of leptin per se on this cognitive domain remains unclear. In this study, we explored the performance of leptin-knockout (leptin-KO) rats in the 5 Choice Serial Reaction Time task (5CSRT), a rodent analogue of the Continuous Performance Test used clinically to assess impulse control and attention. Methods: Male leptin-KO rats (n=7) and wild type controls (n=11) were food restricted under standard conditions and trained in the 5CSRT. Animals learned to respond to a brief light stimulus presented in one of five locations to earn a food reward. Responses made before presentation of the stimulus provided an index of motor impulsivity, while other 5CSRT variables measured attentional ability and motivation to perform the task. Behavioural performance was assessed under baseline conditions, following a 4-week high-fat diet feeding regimen, and after acute amphetamine challenge. Results: Leptin-KO rats showed a mild impairment in learning the task compared to controls; however, once the task was acquired, there were no baseline differences in performance between groups. Prolonged consumption of a high-fat diet had no effect on 5CSRT performance in either group. In contrast, following amphetamine treatment, leptin-KO rats showed enhanced impulsive responding compared to controls, while other behavioural variables remained unchanged. Conclusion: Leptin deficiency slowed the rate at which animals' learned the 5CSRT but did not alter task performance at baseline or after consumption of a high-fat diet. A genotype effect on motor impulsivity was prominently observed after amphetamine treatment, with leptin-KO rats showing potentiated responses; however, the caveat that both groups had been consuming high-fat diet limits our interpretation of these data. Molecular assays of dopaminergic markers are ongoing and may shed light on the mechanisms underlying these results. Thus, leptin deficiency appears to alter impulse control circuits yet further experiments are warranted.

58. **Intra-hippocampal injections of C16 ceramide leads to depressive-like behaviour in mice.** Amato, D. Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany; Reichel, M. Friedrich-

Alexander-University of Erlangen-Nuremberg, Erlangen, Germany; Gulbins, E. University of Duisburg-Essen, Essen, Germany; Kornhuber, J. Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany; Müller, CP. Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany. Background: Major depression is one of the most frequent disorders worldwide. Despite such prevalence, the available treatments are still poor. We have studied the role of the acid sphingomyelinase-ceramide system (Asm-C) as a new target for antidepressants [1]. The Asm-C pathway controls neurogenesis and apoptosis in the brain, which may be altered in depression. Genetically induced ASM (tgASM) overexpression results in a depressive phenotype in mice while genetic ASM deficiency (koASM) abolished these effects. Moreover, therapeutic concentrations of amitriptyline or fluoxetine reduced Asm-C levels. Aim: To further validate the role of Asm-C activity in depression we have investigated the effect of hippocampal microinjections of C16 ceramide on depression-sensitive tests such as the novelty-suppressed feeding, sucrose drinking, forced swim test and coat care in mice. Method: Male C57Bl/6J mice received bilateral injections of either 2 µM/0.2 µl/side C16 ceramide or ghost micelles into the dorsal hippocampus, delivered at 0.1 µl/min flow rate over 2 min. Coat state and novelty-suppressed feeding were scored 7 and 8 days after C16 ceramide injection, respectively. Two more ceramide injections spaced 48h apart were given before sucrose preference was tested on four consecutive days. Their body weight was recorded throughout. Results: C16 ceramide hippocampal injections reduced body weight, prolonged latency to feed, reduced sucrose preference compared to vehicle-treated control, but preserved locomotor activity. Conclusion: Ceramide-injected mice exhibited depression-like symptoms. Decreasing excessive hippocampal ceramide levels may be the main goal of new drugs development with antidepressant activity. References 1. Gulbins, E., et al., Acid sphingomyelinase-ceramide system mediates effects of antidepressant drugs. Nat Med, 2013. 19(7): p. 934-8.

59. **Extended Access to Cocaine Produces Distinct Changes in Homer2 and NPAS4 Gene Expression.** Ploense, K. University of California Santa Barbara: Carr, A. University of California Santa Barbara; Baker-Andresen, D. University of Queensland: Li, X. University of California Irvine: Woodward, N. University of Southern California: Sun, Y. University of California Los Angeles: Bredy, T. University of California Irvine: Kippin, T. University of California Santa Barbara. DNA methylation is a key determinant of gene expression and is implicated in neuroplasticity relevant to addiction. Here, we examine DNA methylation and mRNA expression for two genes, Homer2 and NPAS4, within the dorsal medial prefrontal cortex (dmPFC) following saline, short-access (1h), or prolonged-access (6h), to cocaine during self-administration. As reported previously, only 6h rats exhibited escalated cocaine intake across sessions. Initial MeDIP-CHIP analyses of dmPFC tissue by ChIPMonk software revealed dramatic and extremely gene-specific changes in DNA methylation/demethylation within promoter regions and flanking the transcription start site (TSS). The Homer2 and NPAS4 promoters showed active changes in DNA methylation following 6h and 1h cocaine self-administration compared to saline. A follow-up analysis, via sodium bisulphite conversion followed by mass spectrophotometry interrogating a 1000bp sequence of the Homer2 promoter, confirmed increased methylation of CpG7 in the 6h rats, which contains putative consensus sequences for GATA-1 and p300. Additionally, MeDIP followed by qPCR revealed an increase in DNA methylation for both 1h and 6h rats within the 457-645bp upstream of the NPAS4 transcription start site (TSS).qPCR revealed an increase in Homer2 mRNA levels in the 6h versus 1h and saline conditions, and a decrease in NPAS4 mRNA in 1h and 6h versus saline conditions. These results demonstrate that prolonged cocaine self-administration alters DNA methylation of the Homer2 and NPAS4 gene promoters within the dmPFC in a distinct manner. Additionally, the altered DNA methylation leads to decreases in NPAS4 mRNA and increases in Homer2 mRNA expression within the dmPFC. Given the known roles of Homer2 as a scaffolding protein for the metabotropic glutamate 1 and 5 (mGluR1/5) receptors and NPAS4 as a transcription factor promoting inhibitory synapse formation, these data indicate that excessive cocaine intake induces

changes in gene regulation for inhibitory and excitatory synapses. Thus, excessive cocaine intake induces a distinct change in DNA methylation which may contribute the long-term alterations in brain function associated with addiction.

60. **Oxytocin acts as a potent ethanol antagonist in vivo and in vitro via non-oxytocin receptor mediated blockade of ethanol enhanced activity at GABAA δ subunit containing receptor interfaces.** Bowen, MT. School of Psychology, University of Sydney, Australia. Peters, S. Department of Behavioural and Molecular Neurobiology, University of Regensburg, Germany. Absalom, N. Faculty of Pharmacy, University of Sydney, Australia. Collins (Chebib), M. Faculty of Pharmacy, University of Sydney, Australia. Neumann, ID. Department of Behavioural and Molecular Neurobiology, University of Regensburg, Germany. McGregor, IS. School of Psychology, University of Sydney, Australia. Even moderate doses of alcohol have a considerable impact on motoric function, an effect which is mediated via potentiation of GABAergic activity at GABAA δ subunit containing receptors. Here we demonstrate that oxytocin selectively blocks ethanol induced motoric impairment and ethanol induced increases in GABAergic activity at GABAA δ subunit containing receptor interfaces, an effect which does not involve the oxytocin receptor. Specifically, 1 μg of oxytocin given ICV prior to IP injection with 1.5 g/kg ethanol strongly inhibited the pronounced sedative and myrolexant effects of the ethanol observed in the open field locomotor test, wire hanging test, and righting reflex test. Using two-electrode voltage-clamp electrophysiology we found that oxytocin completely blocked ethanol induced increases in activity at α4β1δ and α4β3δ interfaces. Conversely, ethanol had no effect at α4β1 or α4β3 interfaces, demonstrating that the presence of the α:δ interface is critical for ethanol's effects. Oxytocin had no effect on the motoric impairment or in vitro effects induced by the δ selective GABAA agonist THIP, thus oxytocin's actions are specific to the ethanol binding site at δ containing interfaces. Furthermore, vasopressin (AVP), which is structurally similar to oxytocin, had no impact on the effects of ethanol, confirming that the aforementioned effects are specific to oxytocin and not found with other similar peptides. Finally, our in vitro constructs were not expressing any oxytocin receptors. As such, the observed effects of oxytocin were the result of a non-oxytocin receptor mediated action of oxytocin at GABAA δ containing interfaces. This study reports a profound effect of oxytocin on the behavioural and cellular response to ethanol and provides the first evidence of oxytocin having a direct, non-oxytocin receptor mediated effect on the function of the major inhibitory neurotransmitter system in the central nervous system. This research was supported by NHMRC grants to Prof Collins (Chebib) and Prof McGregor, and a DAAD/Go8 grant to Prof McGregor and Prof Neumann.

61. **Differential involvement of hypothalamus-pituitary-adrenal-axis activity in the effects of enhanced 2-arachidonoylglycerol signaling on responses to social and non-social challenges.** Aliczki, M. Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; Zelena, D. Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; Mikics, E. Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; Varga, ZK. Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; Pinter, O. Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; Venczkone Bakos, N. Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary; Haller, J. Department of Behavioural Neurobiology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary. Enhanced signaling of the endocannabinoid 2-arachidonoylglycerol (2-AG) via blockade of its degrading enzyme monoacilglycerol-lipase (MAGL) exerts robust behavioral effects, however, these effects seem to highly depend on environmental conditions. As the hypothalamus-pituitary-adrenal-axis (HPA) is differentially activated in diverse contexts and it is regulated by endocannabinoid signaling, we

studied its possible involvement in MAGL blockade-induced context-dependent behavioral changes. We presented social (resident-intruder paradigm) and non-social (elevated plus-maze) challenges, respectively, to male CD1 mice, as these situations differentially alter the activity of the HPA-axis. We showed that enhanced 2-AG activity markedly increased basal corticosterone levels, suggesting that basal HPA-axis activity was enhanced by the treatment. When animals faced a non-social challenge, elevated corticosterone levels increased open arm exploration i.e. exerted anxiolytic effects. Interestingly, 2-AG decreased risk assessment behavior as well, suggesting anxiolytic effects as well, but these effects were independent of corticosterone. When animals faced social challenges in the resident-intruder paradigm (either as a "resident" in their home cage or an "intruder" in the home cage of a conspecific, respectively), enhanced 2-AG signaling remarkably decreased aggressive behavior. These behavioral effects were independent of the basal HPA-axis activity-enhancing effects of 2-AG. Our results demonstrate that the HPA-axis is differentially involved in the effects of enhanced 2-AG signaling on responses to social and non-social challenges, respectively. In the former, 2-AG alters the response by an intrinsic mechanism, and abolishes aggressive behavior, while it affects responses to the latter partially via enhanced HPA-axis activity as a secondary effect and causes anxiolysis, however it affects anxiety via direct mechanisms as well.

62. **Effects of chronic unpredictable restraint stress and a post-stress recovery period on spatial learning in male and female rats.** Ortiz, J.B. Department of Psychology, Arizona State University, Tempe, AZ 85287; Campbell, A.N. Department of Psychology, Arizona State University, Tempe, AZ 85287; Hoffman, A.N. Department of Psychology, Arizona State University, Tempe, AZ 85287; Taylor, S.B. Department of Psychology, Arizona State University, Tempe, AZ 85287; Lucas, L.R. Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY 10065; Conrad, C.D. Department of Psychology, Arizona State University, Tempe, AZ 85287. Chronic restraint stress impairs hippocampal-dependent spatial learning and memory in male rats, yet either has no effect or facilitates spatial learning and memory in female rats. Additionally, the spatial learning and memory deficits in chronically stressed males can be reversed following a post-stress recovery period. In males, the deficits produced by chronic stress and the improvement following a recovery period raises the question as to whether a homotypic, predictable restraint stressor contributed to these outcomes. Similarly, a lack of spatial memory deficits in females following a homotypic, predictable restraint stressor raises the question as to whether different results are possible using a paradigm in which restraint becomes unpredictable, or chronic unpredictable restraint (CUR). Using male and female rats, the current study examined the effects of CUR and a post-stress recovery period on spatial learning and memory and limbic glutamic acid decarboxylase (GAD65) expression, a proxy for GABA to assess inhibitory tone. Male (n=30) and female (n=30) adult Sprague-Dawley rats were randomly assigned to either a non-stressed control group (Con), a chronically stressed group (Str-Imm), or a chronically stressed group given a post-stress recovery period (Str-Rec). Stressed rats were restrained over 21 days using daily non-repeated combinations of restraint duration, time of day, locations of where restraint occurred, and exposure to odors. Then, all rats were tested on the radial arm water maze (RAWM) the next day (Str-Imm) or 21 days after CUR ended (Str-Rec). In male Str-Imm rats that were tested immediately after CUR ended, day 1 acquisition of the RAWM was impaired compared to Con rats. This impairment recovered in Str-Rec group. Females did not show significant outcomes following chronic stress or recovery, although the pattern of behavior was consistent with past literature with Str-Imm showing a slight improvement on the retention trial. In males, GAD65 expression within the amygdala negatively correlated with RAWM performance on day 1. In females, day 1 performance positively correlated with GAD65 in the CA1 region of the hippocampus. These results demonstrate that CUR affects spatial learning in a sex-dependent manner with males displaying impaired spatial learning which is reversed following a recovery period. Furthermore, alterations in GABAergic functioning may contribute to the sex differences observed following chronic stress.

63. **Prefrontal GABA-blockade and decision making.** Patrick T. Piantadosi, Shahin Khayambashi, Agnes Cywinska, Magdalen Schluter & Stan Floresco (University of British Columbia, Dept. of Psychology). The prefrontal cortex (PFC) plays a critical role in decision making, and is thought to be an area of pathology in schizophrenia. Individuals with schizophrenia display alterations in cost/benefit decision making involving evaluations of a variety of costs (uncertainty, delays, effort). PFC neurotransmission is thought to be compromised in the disorder, including hypofunction of GABA interneurons. Given that these neurons may be critical for cognitive functioning, we sought to test how decreasing GABA function affects different forms of decision making that are perturbed in schizophrenia. Male rats were well-trained on separate decision making tasks. To assess the impact of GABAergic hypofunction (intended to mimic part of the PFC pathology observed in schizophrenia), rats received intra-medial PFC infusion of the GABA-receptor antagonist bicuculline (50 ng) or saline prior to a test session. On each task, rats chose between one "low-cost" lever that gave an immediate, certain reward (sucrose pellets) after one press, and a "high-cost" lever that delivered a larger reward associated with a form of cost; 1) uncertainty, delivering the reward in a probabilistic manner 2) delays to receiving the reward or 3) requiring more effort to obtain the larger reward. PFC GABA-blockade decreased risky choice, similar to the risk-averse phenotype observed in schizophrenia. This treatment did not affect delay discounting, but did cause a slight decrease in preference for the large/delayed reward when it was not delayed. PFC GABA blockade also slightly reduced the preference for larger rewards associated with greater effort costs. Control experiments suggested that mPFC GABA-blockade does not affect basic motivational process, but does cause mild deficits in preference for larger vs. smaller rewards. GABA-blockade of the mPFC produces discrete alterations in some forms of cost/benefit decision making, some of which may be related to those observed in schizophrenia.

64. **Mechanisms and reversal of adolescent cocaine-induced habits.** DePoy, L.M. & Gourley, S.L. Department of Pediatrics, Emory School of Medicine, Yerkes National Primate Research Center Graduate Program in Neuroscience, Emory University. Adolescence is a period of vulnerability to the development of many psychiatric disorders, including substance dependence disorders that persist across the lifespan. Incubation of certain biological factors associated with addiction may play a causal role. We explored this hypothesis in the context of cocaine-induced stimulus-response habits, which are increasingly considered a causal factor in the development and maintenance of addiction. Here, adolescent or adult mice were exposed to cocaine, and then decision-making strategies were characterized. Mice with a history of subchronic cocaine exposure in adolescence, but not adulthood, developed stimulus-response habits at the expense of engaging in goal-directed decision-making strategies. In addition to these behavioral changes, orbitofrontal prefrontal cortex (oPFC) dendritic spines were eliminated and dendrites were simplified in adults with a history of adolescent cocaine exposure. Stimulus-response habit formation was recapitulated by site-specific infusions of an Abl-family kinase inhibitor STI-571 into the oPFC immediately following response-outcome contingency degradation. Conversely, we show that fasudil, a Rho-kinase inhibitor blocks cocaine-induced habits. Cocaine-induced habits could also be occluded by ifenprodil, an NR2B-selective N-methyl D-aspartate (NMDA) receptor antagonist. Together, these findings suggest that adolescent cocaine exposure confers behavioral vulnerabilities in adulthood by altering cellular structure during adolescent development. Novel treatment strategies should aim to reverse the chronic effects of adolescent cocaine exposure, including behavioral, morphological, and neuroplastic consequences. Supported By: This work was supported by the DA034808, the DA015040, the Emory Egleston Children's Research Center, Children's Healthcare of Atlanta, and the National Center for Research Resources P51RR165 (now the Office of Research Infrastructure Programs/OD P51OD11132).

65. **Whole-body prepulse inhibition protocol for testing in capuchin monkeys: preliminary findings on superior colliculus lesion.** Saletti P. Primate Center and Laboratory of Neurosciences and Behavior, Department of Physiological Sciences, Institute of Biology, University of Brasilia, CEP 70910-900, Brasilia, DF, Brazil; Maior, R. Primate Center and Laboratory of Neurosciences and Behavior, Department of Physiological Sciences, Institute of Biology, University of Brasilia, CEP 70910-900, Brasilia, DF, Brazil; Hori, T. System Emotional Science, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan; Nishijo, H. System Emotional Science, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan; Tomaz, C. Primate Center and Laboratory of Neurosciences and Behavior, Department of Physiological Sciences, Institute of Biology, University of Brasilia, CEP 70910-900, Brasilia, DF, Brazil. Prepulse inhibition is the decrease of startle reflex when a slight stimulus is previously generated. This paradigm may provide valuable information about sensorimotor gating functionality. Here we aimed to determine the startle response of capuchin monkeys (Sapajus spp.), and to evaluate the role of the superior colliculus in prepulse inhibition. Monkeys were tested in a whole-body protocol, to determine the best startle amplitude and interstimuli interval. Additionally we tested two subjects with bilateral superior colliculus (SC) damage in this protocol. Results show that auditory pulse of 115dB has induced the best startle response. Interestingly, no habituation to the auditory stimuli was observed across trials in this species. Also, startle reflex inhibition was optimal after 120msec interstimuli interval. Finally, there was a downward tendency of prepulse inhibition in SC-lesioned monkeys. Our data provides the possibility of further studies with whole-body protocol in capuchin monkeys and reinforces the importance of the superior colliculus in prepulse inhibition.

66. **Neuropsychological functioning in children with sickle cell disease and pica.** Natalia S. David, M.S., Erin T. O'Callaghan, Ph. D., and Jeffrey I. Gold, Ph.D.Objective: Current research has shown that children with chronic illness, such as sickle cell disease (SCD), are at risk for neurocognitive deficits. Amongst the pediatric sickle cell population, 30-40% of children demonstrate pica behavior, which may contribute to medical complications and potentially increase the risk for neurocognitive dysfunction. Despite the high level of correlation and added risk, no research to date has examined the neuropsychological functioning of children with this dual diagnosis. This poster presentation includes an analysis of the neurocognitive and executive functioning of children with SCD.Methods: Seven participants (6males, 1 female; ages 6-11, mean age=8.9 years old) identified to have SCD (57% HbSS, 29% HbSC, 14% alpha-thalassemia) were recruited as part of a larger pilot study examining eating habits of children with SCD. All participants' cognitive functioning was assessed using the two-subtest form of the WASI. Executive functioning was assessed using several subtests from the D-KEFS and NEPSY-II. Relevant medical data (i.e. hemoglobin level, lead level, hospitalization history) was obtained from medical charts, and pica behavior was assessed through parent and self-report. Results: Results of cognitive testing revealed FSIQ scores ranging from profound impairment to average. All children demonstrated difficulty in executive functioning tasks, ranging from profound impairment to high average performance. A discussion of each participant's relevant medical and pica history will be provided. Conclusions: This is the first known investigation of neuropsychological functioning in children with SCD and pica. These preliminary results reveal scores that support our original hypothesis that pica behavior may increase the risk for neuropsychological deficits. A more detailed comparison of the cognitive and executive functioning performance of these children, as well as a discussion on the potential implications of pica behavior on academic and social functioning will be provided.

67. **Screening for autism in preterm children with birth weights less than 1500 g.** Iva Dudova (1), Martina Kasparova (2), Daniela Markova (3), Jana Zemankova (4), Stepanka Beranova (1), Tomas Urbanek (5), Michal Hrdlicka (1); (1) Department of Child Psychiatry, Charles University Second Faculty of Medicine and University Hospital Motol, Prague, Czech Republic; (2) Department of

Pediatrics, Charles University Second Faculty of Medicine and University Hospital Motol, Prague, Czech Republic; (3) Department of Pediatrics and Adolescent Medicine, Charles University First Faculty of Medicine and General University Hospital, Prague, Czech Republic; (4) Department of Pediatrics, Charles University Faculty of Medicine and University Hospital, Hradec Kralove, Czech Republic; (5) Institute of Psychology, Academy of Sciences, Brno, Czech Republic. Introduction: Multiple studies of children with very low (VLBW; 1000 – 1500 g) and extremely low (ELBW; under 1000 g) birth weight have indicated that this population seems to have a higher risk of autism spectrum disorders (ASD) relative to children with normal birth weights (≈ 1.14%). Recent studies on this topic have described the prevalence of ASD among prematurely born children to be in the range of 3.65 – 12.9%. Methods: Parents of 115 VLBW and ELBW children (age 2 years, corrected for prematurity; 64 boys, 51 girls) completed screening questionnaires. The screening battery included the Modified Checklist for Autism in Toddlers (M-CHAT), Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist (CSBS-DP-ITC), and the Infant/Toddler Sensory Profile (ITSP). All children who screened positive on any of the screening tools were subsequently assessed using the ADOS (Autism Diagnostic Observation Schedule). Results: Forty three children (37.4%) screened positive on at least one of the parental administered screening questionnaires. The screening tool with the most positive results was the CSBS-DP-ITC (35 positive screens), followed by the M-CHAT (22 positive screens) and the ITSP (14 positive screens). Differences in the frequency of positive screens among the tests were significant ($p = 0.001$). Of the 43 children who tested positive, 27 participated in the detailed ADOS follow-up assessment. A diagnosis of ASD was confirmed in 11 of the 27 children. ASD prevalence, calculated from those 27 children and those with negative screening results (72 children), yielded an ASD prevalence of 11.1% of the sample. Conclusions: The results strongly support the hypothesis that there is a higher prevalence of autism in children with birth weights less than 1500 g. Additionally, we found that the simultaneous use of multiple screening tests increases screening sensitivity. Acknowledgments: Supported by Ministry of Education, Youth and Sports, Czech Republic (research grant COST LD11028), Ministry of Health, Czech Republic (conceptual development of research organization, University Hospital Motol, Prague, Czech Republic 00064203), and by the ESF (COST Action ESSEA BM1004).

68. **Memory impairment of APP-transgenic mice in pre-amyloid stage is linked to a reduced support of formation of neuronal processes in the hippocampal neurogenic niche.** Bozena Mazur-Kolecka1, Giuseppe Lafauci1, Richard Rubenstein2, Wojciech Kaczmarski1, Janusz Frackowiak1. Reduced adult neurogenesis has been implicated in learning and memory deficit in neurodegenerative diseases with amyloid-b peptide (Ab) deposition. Neurotoxicity of fibrillar Ab deposited in neurogenic areas in brain seems to be responsible for neuronal loss and impaired neurogenesis. However, the mechanisms by which soluble factors in local brain environment in amyloidosis-b influence the pool of neuronal progenitors (NP) and their differentiation are not well understood. We studied the influence of extracts from hippocampus—the neurogenic area in adult brain— from Tg9291 mice with human Ab precursor protein 695 (APP) with the Swedish, Dutch and London mutations with memory deficits on NP proliferation and maturation in culture. Tg9291 mice showed learning and memory impairments that start at 4 month of age and progress up to 9 month, as revealed in the Morris water maze test after 3 and 5 days of training for finding a submerged platform, and by the memory retention test. Extracellular Ab deposits in the hippocampi were detected at 6-7 months of age. Hippocampal extracts were prepared from 3-4 month-old Tg9291 mice; i.e., during development of learning and memory deficit but before amyloid- deposition in the hippocampus. The extracts from Tg9291 mice over-expressed N- and C-terminal-APP, Ab40 and Ab42, as tested by immunoblotting. The ability of soluble factors present in hippocampi to support proliferation and neuronal differentiation of NP was tested in cultures supplemented with 20ug/ml extracts. Proliferation of NP was significantly stimulated by extracts from both control and transgenic mice after 24 hours, as tested by BrdU-incorporation. This suggests a

supportive function of the local environment in the hippocampus on maintaining the NP pool which is similar in the Tg9291 and in control mice. After 7 days' cultures the NP treated with extracts from Tg9291 mice generated less small neurons migrating from neurospheres. The ability to form dendrite trees by these cells was reduced, as evaluated by immunofluorescence in confocal system and morphometry. The results suggest that learning and memory deficits in Tg9291 mice before development of amyloidosis in hippocampi may result from impaired neurogenesis and neurite development in the dentate gyrus enriched in APP and its fragments. Deteriorating effect of the local environment on neurogenesis may explain lack of spontaneous neuroregeneration in amyloidosis-b. Sponsored by NYS OPWDD

69. **The impact of brain levels of monomeric A□ and Cdk5 activation on learning and memory impairment in mouse models of brain amyloidosis-beta.** J. Frackowiak1, B. Ranasinghe1, G. Lafauci1, R. Rubenstein2 , R. Kolecki1, W. Kaczmarski1, B. Mazur-Kolecka1. Impairment of memory in Down syndrome and in Alzheimer's disease is caused by neurodegeneration and by deficient neurogenesis in the hippocampus. Studies in mouse models have shown that deficits of memory functions follow accumulation of oligomeric A□ even without neurodegeneration. The pathomechanisms triggered by A□ that lead to memory deficits remain controversial. Some effects of A□ may be mediated by activation of cysteine proteases which cleave p35—the activator of Cyclin-dependent kinase-5 (Cdk5) —into p25. Binding of p25to Cdk5 increases the kinase activity of the complex, alters its cellular location and may lead to abnormalities of neuronal structure, maturation and synaptic plasticity. We tested development of learning and memory impairment in mouse strains Tg9279 and Tg9294 with different copy numbers of human APP transgene with the Swedish, Dutch and London mutations. Learning and memory were evaluated by the Morris water maze test. Brain levels of APP, A□, Cdk5, p35 and p25 were detected by WB. Proliferating neuroprogenitor cells were detected in the hippocampus by immunostaining for Ki67. The brain levels of transgenic APP at 3 month of age were 2 times higher in Tg9279 than in Tg9294. Frontal cortex levels of A□1-40 and A□1-42 in Tg9279 were 8.4 and 7.2fmol/100□g protein, respectively, both were monomeric. The respective A□ levels in Tg9294 mice were 40-45% of these values. Proliferation of neuronal progenitor cells in the dentate gyrus in the hippocampus was not reduced in the transgenic mice. Learning and memory were significantly impaired in homozygous Tg9279 mice at the age of 13 weeks, prior to formation of amyloid deposits in the hippocampus. The onset of amyloidosis-□ in Tg9294 mice was 12 months, but significant learning and memory deficits were observed at 9 months of age. At that time the levels of A□1-40 increased to 6.2 fmol/100□g protein and about 60% of it was dimeric. The APP transgene and increased brain levels of A□ did not modify brain expression of Cdk5. Higher levels of p25 in the hippocampus coincided with impairment of learning and memory. We propose that learning and memory deficits appear as the levels of monomeric or oligomeric A□ reach the levels sufficient to dysregulate processing of p35. Accumulation of the Cdk5/p25 complex with high kinase activity in the hippocampus may lead to dysfunction of the newly generated neurons in the dentate gyrus. Supported by funds from NYS OMRDD.

70. **Title: The efficacy of cold facial immersion and the diving response in treating panic disorderr.** Peter Kyriakoulis, Prof. Mike Kyrios, Prof. David liley, Dr. Mark Schier. A useful paradigm to study panic and anxiety is inhalation of carbon dioxide CO2. According to the literature, patients that suffer from panic disorder are likely to produce the panic symptoms when they inhale a single deep breath of CO2. One of the common biological theories of the CO2 responsivity theory proposed by Klein posited that panic disorder patients are more likely to experience a false alarm consequently due to their increased sensitivity of their chemical chemoreceptors, resulting in dyspnea and elevated heart rate. Ziemann et al 2009, found during preclinical investigations that an acid –sensing ion channel in the amygdala has been identified as playing a key role as a vital chemosensor for hypercapnia eliciting fear

responses. Administration of CO2 leads to a "complex brain fear network including the amygdala, the hippocampus, and the medial prefrontal cortex" (Gorman et al, 2000, 2001). This study examined whether CO2 sensitivity in panic disorder differs from that of normal patients. Normal participants and panic disorder participants undertook a series of challenge provocation tests including a breath hold task, a 35% single breath CO2 inhalation and a cold facial immersion task before and following a 35% single breath CO2 inhalation, to assist in better understanding the pathophysiology of panic disorder and to determine how these two groups of participants differ in these challenge provocation tasks. It was found that panic patients differed in breath hold time than normal participants. Furthermore the study also examined the activation of the diving response before and after CO2 administration. This adaptive diving reflex which is found in all mammals is triggered specifically by cold water contacting the face. Upon initiation of the reflex the physiological changes include a decrease in heartbeat (bradycardia), constriction of blood vessels in certain parts of the body (vascular constriction), increased blood pressure, and the spleen contracts to release more oxygen carrying red blood cells into bloodstream. The study found that the cold facial immersion following the 35% CO2 inhalation was lower, suggesting that it may have implications as a future treatment for panic disorder. Long term training of breath hold diving or apnea is associated with several physiological adaptations including a more pronounced diving response, than untrained control subjects (Schagatay and Anderson , 199; Ferretti and Costa, 2003).

71. **Predator odor- induced fear: A behavioral characterization and neural substrate analysis.** Wernecke, K. 1,4; Vincenz, D. 2,4; Storsberg, S. 3,4; Goldschmidt, J. 2,4; D'Hanis, W. 3,4; Fendt, M. 1,4; 1 Institute for Pharmacology and Toxicology, Otto-von-Guericke-University, Magdeburg, Germany; 2 Leibniz Institute for Neurobiology, Magdeburg, Germany; 3 Institute for Anatomy, Magdeburg, Germany; 4 Center for Behavioral Brain Sciences, Magdeburg, Germany. Predator odors such as carnivore urine represent a group of biologically-relevant chemosignals that enable prey animals to earlier recognize predatory threats in their environment and to initiate appropriate defensive responses against it. Although the behavioral repertoire of anti-predatory responses (e.g. escape/avoidance, reduction in locomotor activity, risk assessment, ultrasonic vocalization) has been described extensively, our knowledge about the neural circuitries mediating these innate fear responses is rather poor. Previously, we showed that Sprague-Dawley rats displayed robust fear-like behavior, evidenced by increased avoidance and risk assessment when exposed to urine samples of different carnivores (e.g., fox, wolf, mountain lion, bobcat). By means of combined methods from behavioral neuropharmacology, neural imaging and immunohistochemistry, we are now investigating the neural basis underlying predator odor- induced defensive behaviors. Here, using in vivo single-photon emission computed tomography (SPECT) imaging of regional cerebral blood flow, we present data showing that exposure to fox urine modulates neural activity in numerous structures including parts of the posterior amygdala, piriform cortex, habenula and interpeduncular nucleus. Consistent with these data, we further show that the temporary inactivation of the posterior amygdala and presumably of the habenula by local administration of muscimol practically abolish fox urine-induced avoidance behavior. In order to further behaviorally characterize the effects of biologically-relevant odors, we developed an olfactory version of the hole-board test. This experimental set-up is especially advantageous because it allows us to study the effects of up to four different olfactory cues on rat's behavior in a single one-trial test. First data demonstrate, that the number of head dips into holes "baited" with a predator odor sample is remarkably reduced when compared to the number of visits of the control odor hole. At the same time, animals visit more often the hole containing a urine sample of an estrous rat. Currently, we are testing whether anxiolytic-like manipulations specifically modulate the visits of "predator odor-baited holes", but not of "control/ female odor-baited holes".

72. **Spatial long-term memory and modulation of NMDA receptor subunit expression in medial septal immunolesioned rats.** Naneishvili T.[1,2], Dashniani M.[1], Burjanadze M.[1], Chkhikvishvili N.[1], Beselia

G.[1], Chighladze M.[2] [1] I. Beritashvili Center of Experimental Biomedicine, 14 Gotua Street, 0160 Tbilisi, Georgia; [2] St.Andrew the Firs-Called Georgian University of Georgian Patriarchate, 53a Chavchvadze av. 0162 Tbilisi, Georgia. The present study was designed to investigate the effect of selective immunolesions of cholinergic and GABA-ergic SH projection neurons (using 192 IgG-saporin and GAT-1 saporin, respectively) on spatial memory assessed in MWM and NMDA receptor GluN2B subunit expression in the rat hippocampus. We used MWM training protocol with eight training trials. One day after training, probe test with the platform removed was performed to examine long-term spatial memory retrieval. We found that immunolesion of medial septal cholinergic neurons did not affect spatial learning as exhibited by a decreased latency to find the hidden platform across the eight training trials. In contrast, rats with immunolesions of medial septal GABAergic neurons did not show a decreased latency across training trials in MWM. Trained control rats spent significantly longer than chance (15 s) performances such as swimming time in test sector (where the hidden platform was located). Moreover, they spent significantly longer in test sector than in the opposite sector, confirming the establishment of long-term memory. In contrast, the preference for test sector was abolished in medial septal immunolesioned rats. Because Saporin treated rats learned the location of the hidden platform during training, the results suggest that saporin treated rats could not remember the training a day later. We found that the expression level of NR2B subunit of NMDA receptor in the hippocampus was decreased significantly in the GAT-1 treated group compared with the control and saporin treated groups. In conclusion, our findings suggest that immunolesion of medial septal GABAergic neurons can interrupt hippocampus ‐ dependent spatial learning, possibly through modulation of NMDA receptor subunit expression in the hippocampus. Moreover, our finding that selective lesions of medial septal cholinergic neurons affects probe-test performance but not spatial learning, suggests that septohippocampal cholinergic projections are involved specifically in the consolidation or retrieval, but not in the acquisition of long-term spatial memory.

73. **Nucleus accumbens response to palatable food positively correlates to subjective food craving score in overweight subjects.** Yuko Nakamura The John B. Pierce Laboratory, Dana M Small The John B. Pierce Laboratory, Department of Psychiatry, Yale School of Medicine, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases. Obesity is associated with functional impairments in discrete brain regions and neurotransmitter systems. Specifically, imaging experiments have shown abnormalities in brain glucose metabolism in the striatum of obese humans (Michaelides et al. 2012). Further high body mass index (BMI) is associated with increased dopamine D2/3 receptor binding potential in the ventral striatum, which plays an important role in motivation and feeding (Caravaggio et al. 2013). Obese people excessively seek high-calorie, palatable food and this behavior is hypothesized to depend on the above-mentioned brain abnormalities (Volkow et al. 2014). In order to examine the relationship between food craving and the brain response to palatable food, we performed a functional magnetic resonance imaging (fMRI) on 39 overweight (BMI $\geq$ 25; average, 28.6; SD = 3.1) and 34 lean subjects (BMI < 25; average, 22.2; SD = 1.6). We measured the brain response to a palatable food (milkshake) and collected self-reported desire to consume the palatable food ("wanting") that assessed the subjects' desire for this stimulus. We observed a robust positive relationship between the ventral striatum (nucleus accumbens [NAc]) response to the milkshake and the "wanting" score in overweight subjects [p(FWE-corrected) = 0.021, z = 3.31]. No such relationship was observed in the lean subjects. The relationship between increased NAc response and "wanting" in overweight subjects suggests that enhanced reward circuit reactivity to palatable food in this population could predict future craving and drive overeating.

74. **Impaired attentional selectivity in rats with subthalamic nucleus lesions.** Xia, S. University of St Andrews; Tait, D. University of St Andrews; Brown, V. University of St Andrews;. Executive functions are mediated by the interplay of cortical and subcortical structures and in particular the basal-ganglia-

thalamo-cortical loops. Prefrontal cortical projects to the subthalamic nucleus are one of the key inputs to the basal ganglia. It is therefore plausible to suggest that the STN is implicated in executive functions. As anatomical and behavioural studies have suggested that the STN is involved in response inhibition, we tested the hypothesis that the STN may also be inhibitory in the cognitive domain. We tested rats in the standard 7-stage attention set-shifting task. This task includes reversal learning stages, which require inhibiting previously rewarded responses. It also includes an attentional set shift, which required inhibition of attention to previously relevant stimulus characteristics. Rats with STN lesions were not impaired on acquisition of discriminations and, interestingly, were also not impaired on reversal learning: STN-lesioned rats are able to inhibit previously rewarded responses. Not only were the rats not impaired on acquisition at the ED stage, they were better than controls at this stage, and worse than controls at the ID stage. This lack of difference between ID and ED is indicative of a failure of form an attentional set. Subsequent experiments tested different hypotheses to account for this behavioural pattern. Rats with STN lesions could remember a discrimination even after several intervening stages, indicating that memory for the reinforcement history was intact. In a probe stage in which the irrelevant dimension was changed after acquisition, control rats were not distracted but lesioned rats had to re-learn the new stimuli. In addition, performance was facilitated in a bi-conditional discrimination. We interpret these results to mean that set-formation following STN-lesions is impaired due to an attentional deficit that limited the animals' attentional selectivity.

75. **Long term effects of stress block aversive effects of kappa opioid receptors.** Laman-Maharg, A. Department of Psychology, Neuroscience Graduate Group, and Center for Neuroscience, University of California, Davis, CA, USA; Campi, KL. Department of Psychology, University of California, Davis, CA, USA; Manning, CE. Department of Psychology, University of California, Davis, CA, USA; McMackin, MZ. Department of Molecular Biosciences and Molecular, Cellular and Integrative Physiology Graduate Group, University of California, Davis, CA, USA; Robles, CF. Department of Psychology, University of California, Davis, CA, USA and Department of Psychology, Michigan State University, East Lansing, MI, USA; Takahashi, EY. Department of Psychology, University of California, Davis, CA, USA; Trainor, BC. Department of Psychology, Center for Neuroscience, Neuroscience Graduate Group, and Molecular, Cellular and Integrative Physiology Graduate Group, University of California, Davis, CA, USA. Psychosocial stress leads to activation of kappa opioid receptors which in turn facilitate depression-like behaviors. This has generated a strong interest in the development of KOR antagonists as a potential novel class of antidepressant. However, new evidence suggests that there is a major gap in our understanding of the aversive properties of KOR. The overwhelming majority of studies examining stress-induced activation of KOR have focused on short-term effects of stress. In contrast social defeat stress induces changes in brain and behavior that last for weeks or months. Here we show that a long term effect of defeat stress is that the KOR agonist U50,488 loses its aversive properties. In female California mice (Peromyscus californicus) naïve to defeat, place conditioning with 2.5 mg/kg of U50,488 induced a significant place aversion. In contrast, female California mice exposed to social defeat did not form a place aversion at this dose. Similarly, a single injection of U50,488 reduces social interaction behavior in female California mice naïve to defeat. Social defeat stress also reduces social interaction behavior in female California mice, but a single injection of U50,488 treatment blocks this effect. Social defeat had no effect on dynorphin mRNA but reduced KOR mRNA in the nucleus accumbens, suggesting that defeat may induce desensitization to KOR. Ongoing studies are testing this hypothesis. These data suggest that KOR agonists could prove useful for treating stress-induced psychiatric disorders.

76. **Acute inflammatory pain and DNA methyltransferases.** Abzianidze E.[1]; Kvaratskhelia E. [1]; Tkemaladze T[1]; Gurtskaia, G. I.[2]; Nebieridze M. I.[2]; Nozadze L. I.[2]; Tsagareli M. G. I.[2] [1]Tbilisi State Medical University, Department. of Molecular and Medical Genetics; [2]Beritashvili Centre of

Experimental Biomedicine, Dept of Pain and Analgesia. Aim of Investigation: Pain is the most unpleasant symptom of illness, which is mediated by a variety agents released from local inflammatory cells. Recent studies points to the involvement of epigenetic mechanisms both in the development and maintenance of pain states. One of the most fundamental epigenetic marks is the methylation of cytosine residues in DNA, catalyzed by DNA-methyltransferase enzymes. The aim of the present study was to analyze the changes of DNMT1, DNMT3a and DNMT3b in the trigeminal ganglia (TG) neurons during the maintenance phase of pain states. Methods: Mustard oil (10%) or capsaicin at concentrations of 0.4%,- 0.6% (Sigma-Aldrich, USA) was applied to four- month-age male rats to induce acute inflammatory pain and responses to mechanical stimuli were assessed. All animal studies confirmed to the Guidelines of International Association for the study of Pain regarding investigations. The levels of DNMT1, DNMT3a and DNMT3b were measured in nuclear extracts of Trigeminal ganglia (TGs) neurons in study and control groups. DNMTs assay kits were used to measure the amount of DNA-methyltransferases. Results and Conclusions: Mustard oil-evoked pain increased the levels of DNMT3a and DNMT3b, Mustard oil has no significant effect on levels of DNMT1, while capsaicin induced pain increased the levels of DNMT3a and DNMT3b,as well as levels of DNMT1, in the same regions compare to control sample. This study provides the evidence that epigenetic modification,such as DNA methylation plays a role in development of pain in animal models. Epigenetic analysis may identify mechanisms critical to the transition from acute to persistent pain.

77. **Repeated treatment with the D1 agonist SKF81297 yields impairment of object memory in rats.** Taukulis, H., Department of Psychology, University of New Brunswick, Saint John, NB, Canada; Ilkay, J., Department of Psychology, University of New Brunswick, Saint John, NB, Canada. A regimen of repeated treatment with methylphenidate (Ritalin) has been found to yield deficits in some types of memory tasks in rats, notably object recognition and spatial memory. Methylphenidate is a dopamine and norepinephrine reuptake inhibitor. It has been hypothesized that increased levels of synaptic dopamine and the resultant hyper-stimulation of D1 dopamine receptors may account for this impairment. This is supported by evidence that the blockade of these receptors by the selective antagonist SCH23390 30 min prior to each dose of methylphenidate prevents this effect, and the treated rats remember objects in normal fashion. To further implicate D1 receptors in the methylphenidate-induced loss of object memory, a highly selective agonist of the D1 receptor subtype, SKF81297 (0.15 and 0.30 mg/kg, i.p.) was administered to male and female rats once per day for 21 days, beginning at PN30. After a 14-day washout interval, the animals were found to exhibit memory deficits like those elicited by chronic methylphenidate, thereby lending weight to the D1 hyper-stimulation hypothesis.

Friday, June 13

8:00-10:00 **Symposia: Current advances in animal models of neurodevelopmental disorder**s. Chair: Mu Yang

Advanced Assays for Therapeutic Development in Models of Autism. JL Silverman, MC Pride, JE Hayes, JN Crawley. Neurodevelopmental disorders, such as autism and fragile X syndrome, were long thought to be medically untreatable, on the assumption that brain dysfunctions were hardwired before diagnosis. Recent findings that many cases of autism are linked to mutations in genes that control formation and maturation of synapses in adult brains have challenged these principles. Dysregulation of the excitatory/inhibitory balance in the brain has been hypothesized as a possible cause of autism. Reducing excitatory glutamatergic transmission, and/or elevating GABAergic inhibition, could normalize the excitatory/inhibitory balance and reverse autism-relevant phenotypes. This theory is supported by electrophysiological studies in mouse models with mutations in risk genes for autism, in which excessive glutamatergic excitation or impairments in synaptic plasticity are common. Furthermore, clinical trials of positive and negative modulators of glutamatergic and GABAergic receptors are being pursued. Our specific objective is to test the hypothesis that modulation of excitatory/inhibitory balance could reduce high levels of repetitive behavior and improve sociability, using high-throughput automated assays in mouse models of non-syndromic autism with high face validity. The results shown in this presentation will focus on mGluR modulators and a GABAB agonist compound. Our findings raise the possibility that targeted pharmacological interventions may alleviate one or more of the core behavioral symptoms of autism.

Alterations in cortical firing and executive control deficits after prenatal alcohol exposure. K. Marquardt, R. Sigdel and J.L. Brigman. Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM 87131-0001, USA. An increasing body of literature suggests that even low to moderate prenatal alcohol exposure (PAE) may result cognitive deficits that persist throughout the lifespan. Clinically, these deficits are categorized as Fetal Alcohol Spectrum Disorders and can include impairments in learning and memory, social behavior and particularly, executive function. Executive function encompasses a broad range of cortically mediated behaviors including working memory, response inhibition and behavioral flexibility. Not surprisingly, impairments in executive control reduce quality of life by negatively influencing employment, finance management and maintaining relationships. It has been shown that high doses of PAE can impair executive control in rodent models and recently we have demonstrated that even moderate PAE is sufficient to impair behavioral flexibility in adult mice. In order to explore whether these behavioral deficits were mediated by alterations in cortical neuronal activity we performed in vivo electrophysiology in PAE and saccharine control (SAC) mice. Recordings were performed in the lateral orbitofrontal cortex (lOFC), a region known to mediate flexible behavior across species and previously established to be functionally necessary for reversal learning on our paradigm. Results of these experiments showed that moderate PAE altered firing in the lOFC specifically during early reversal, where behavior is most impaired in these mice. Specifically, PAE mice showed significantly reduced baseline firing rates during this critical period. Given this evidence and recent findings that direct stimulation of cortical firing is sufficient to restore cortical control we are now examining whether increasing lOFC firing via lentiviral expression of channelrhodopsin and light stimulation given during choice behavior is sufficient to restore behavioral flexibility after PAE. Our data demonstrates the utility of coupling in vivo electrophysiology, optogenetics and touch-screen learning tasks to explore the underlying neuronal function of cognitive deficits. Using these methods we established that a long lasting impairment in executive function after moderate PAE may be the result of decreased cortical firing.

A nonhuman primate model of maternal immune activation. Melissa D. Bauman, University of California, Davis. Maternal infection during pregnancy is associated with an increased risk of having a child later develop a neurodevelopmental disorder, such as autism or schizophrenia. In a mouse model of maternal immune

activation (MIA), administration of the viral mimic dsRNA poly(I:C) to pregnant dams results in offspring with increased anxiety and repetitive behaviors as well as deficits in social interaction and communication. To further evaluate this risk factor, we have adapted the rodent polyI:C model for use in the nonhuman primate. A modified form of poly(I:C) was delivered to pregnant rhesus monkeys (Macaca mulatta) at the end of either the first or second trimester. A separate control group of pregnant rhesus monkeys received saline injections at these time points. Behavioral development of the MIA-exposed macaque offspring was then systematically evaluated for the first 4 years of life. MIA in the nonhuman primate model was associated with alterations in brain, behavior and immunological development that resemble features of human neurodevelopmental disorders.

Engineered deafness reveals that mouse courtship vocalizations do not require auditory experience. Elena Mahrt, Washington State University Vancouver; Ling Tong, University of Washington; David Perkel, University of Washington; Edwin Rubel, University of Washington; Christine Portfors, Washington State University Vancouver. Auditory experience during development is necessary for normal language acquisition in humans. Although songbirds, some cetaceans, and maybe bats may also be vocal learners, vocal learning has yet to be well established for a laboratory mammal. Mice are potentially an excellent model organism for studying mechanisms underlying vocal communication. Mice vocalize in different social contexts, yet whether they learn their vocalizations has been controversial. To address this question, we compared ultrasonic courtship vocalizations emitted by chronically deaf and normal hearing adult male mice. We deafened CBA/CaJ male mice, engineered to express diphtheria toxin receptors (DTRs) in hair cells, by systemic injection of diphtheria toxin (DT) at postnatal day (P)2. By P9, almost all inner hair cells were absent and by P16 all inner and outer hair cells were absent in DTR mice. These mice did not show any auditory brainstem response (ABR) as adults. Wild-type litter-mates, also treated with DT at P2, had normal hair cells and normal ABRs. We compared the temporal structure of vocalization bouts, the types of vocalizations, the patterns of syllables, and the acoustic features of each syllable type emitted by hearing and deaf males in the presence of a female. We found that almost all of the vocalization features we examined were similar in hearing and deaf animals. These findings indicate that mice do not need auditory experience during development to produce normal ultrasonic vocalizations in adulthood. We conclude that mouse courtship vocalizations are not acquired through auditory feedback-dependent learning.

8:00-10:00 **Symposia: Deep brain stimulation of the basal ganglia nuclei: Animal and human studies.**
Chair: Claudio Da Cunha

The role of the basal ganglia in action-selection. Claudio Da Cunha, Universidade Federal do Paraná, Curitiba, PR, Brazil. The basal ganglia (BG) is one of the few brain systems where the known circuitry can explain its role: selection of all aspects of behavior. The repertoire of motor responses programmed in the motor cortex can be activated by neurons of the motor thalamus (e.g. VLo) which, in turn, are under tonic inhibition of the output stations of the BG (e.g. pallidal and pars reticulata nigral neurons). Moment by moment neurons in the striatum (the main input station of the BG) use information uploaded from cortical and subcortical areas of the brain to select which motor response is the best choice to get a reward or to avoid aversive outcomes. Release of dopamine in the striatum by midbrain neurons optimizes the action selection accuracy and provides a teaching signal (a reward prediction error signal) to improve future choices. This view evolved from different biological, clinical, and computational approaches which will be reviewed here. In addition, the speaker will present literature and recent data he himself has collected supporting the view that projection neurons of the striatum encode motor actions of specific body parts towards specific objects as proposed by the "Mosaic of Broken Mirrors Model" (Behav Brain Res 199:156-169, 2009). This introduction to the role of the BG in action selection will pave the way for the understanding of how deep brain stimulation can alleviate symptoms of some of the BG diseases. These will be addressed by the next panelists.

Simultaneous Neurochemical Sensing, Stimulation, and fMRI Studies Using WINCS Harmoni During Deep Brain Stimulation. Kendall H. Lee, MD, PhD, Allan J. Bieber, Ph.D., and Kevin E. Bennet, MBA. Mayo Neural Engineering Laboratories. Despite its clinical success in variety of neurologic and psychiatric disorders, there is a limited understanding of the therapeutic mechanism behind Deep Brain Stimulation (DBS). To fully understand the neurochemical and neural circuit effects of DBS, we developed the WINCS (Wireless Instantaneous Neurochemical Concentration Sensing system), MINCS (Mayo Investigational Neuromodulation Control System), and fMRI monitoring during DBS. WINCS employs fast scan cyclic voltammetry (FSCV) to characterize the neurochemical interactions events during DBS and MINCS allows wirelessly controlled electrical stimulation. Presently, we have developed a second-generation electrochemical monitoring and stimulation system called WINCS Harmoni. WINCS Harmoni incorporates a wirelessly controlled synchronizable neurostimulator, and four-channel integrated circuit for simultaneous neurochemical and electrophysiological measurements. PC based software provides real-time control of stimulation, neurotransmitter detection, data acquisition, and data visualization. We demonstrate Harmoni's 4-channel capability to accurately detect disease-relevant analytes. Additionally, we also examined Harmoni's efficacy in vivo using a bipolar stimulation electrodes placed in the medial forebrain bundle (MFB). Harmoni successfully evoked and detected striatal dopamine release by DBS. Notably, the synchronization of stimulation with interleaved FSCV scans eliminated the stimulus artifact that would have otherwise obscured the neurochemical measurements. In addition, the stereotactic targeting of the recording electrode was identified by fMRI BOLD activation during DBS in the pig, monkey, and human. Taken together, our results suggest the activation during DBS corresponds to neurotransmitter release in distant sites of the neural circuit. In future work, we anticipate the use of feedback loop smart DBS system that incorporates electrochemical sensing.

Subsecond release of striatal DA after stimulation of subthalamic nucleus: animal and human studies. Charles D. Blaha, Department of Psychology, University of Memphis, Memphis, TN 38152. Cutting edge electrochemical techniques applied in animal and human studies of basal ganglia (striatal) functioning have shown great promise in understanding the neuronal circuitry and mechanisms by which deep brain stimulation (DBS) improves Parkinson's disease (PD) motor disabilities. DBS targeting of the subthalamic nucleus (STN) is well known as an effective neurosurgical approach for treating PD motor disabilities and is most effective in patients who respond well to L-dopa. These clinical observations suggest that STN DBS functions to augment the pharmacological effectiveness of L-dopa and that an increase in striatal DA may, in part, account for the therapeutic efficacy of STN DBS. In this regard, therapeutic outcomes of DBS surgeries have suggested that the best improvement in symptoms is obtained when the DBS electrode projects onto white matter just dorsal to the STN, the DA axons within the medial forebrain bundle (MFB) which project to the striatum. While the mechanisms of STN DBS currently remain unknown, together with these clinical observations, and from a number of studies in intact and lesioned animals, we have suggested that the therapeutic benefit of STN DBS may be mediated, at least in part, by activation of surviving nigrostriatal DA neurons (Lee et al. 2011). In addition, the pedunculopontine tegmental nucleus (PPT) has also served as a target for DBS to improve deficits in posture and gate. PPT DBS can also influence striatal DA release by activating DA cells in the substantia nigra (SN) via direct excitatory cholinergic and glutamatergic afferents, as well as indirectly through excitatory cholinergic and glutamatergic projections to the STN which, in turn, sends glutamatergic projections to SN DA cells. Data will be presented suggesting that activation of ascending SN DA axons by STN DBS may be mediated by direct MFB stimulation, as well as directly via excitatory glutamatergic and cholinergic inputs to SNc dopamine cells, and as well as indirectly through inputs to SNc DA cells via excitatory cholinergic and glutamatergic STN-PPT-SNc pathways. Understanding of the underlying neural mechanisms and circuitry of STN DBS could lead to the elucidation of optimal stimulation locations and parameters which may prove invaluable in refining DBS procedures and enhancing the clinical efficacy of DBS. Lee, KH et al. 2011. Emerging techniques for elucidating mechanism of action of deep brain stimulation. Engineer. Med. & Biol. Soc. 25:677-80.

Mapping the functional neural network of deep brain stimulation using fMRI. Paul Hoon-Ki Min, Mayo Clinic, MN. Deep brain stimulation is a well-established therapy for a variety of movement disorders such as Parkinson's disease, essential tremor, and dystonia. It is also an emerging therapy for several psychiatric and neurological conditions, including epilepsy, Tourette's syndrome, major depression, and obsessive compulsive disorder. Although the underlying pathophysiology of these disorders and mechanisms of stimulation-induced neuromodulation are not completely understood, we know that modification of pathological states by DBS depends on targeting specific sites in the complex neuronal circuitry underlying them. Functional imaging techniques, including functional magnetic resonance imaging (fMRI), Positron Emission Tomography (PET), and Single-Photon Emission Computed Tomography (SPECT), have emerged as powerful tools in the study of the DBS-induced changes in neural activity. Implementation of these imaging techniques in the clinical setting, as well as in large animal research, has begun to shed light on the neural networks associated with diverse disease states and which are crucial for the therapeutic effects of DBS. Here, we discuss the results from fMRI studies of DBS effects in large animals and human patients undergoing DBS. We discuss the functional implications of DBS of the subthalamic nucleus (STN) and globus pallidus internus (GPi) for Parkinson's disease, and on its effect on thalamocortical basal ganglia circuit. These data provide strong evidence that functional imaging constitutes a powerful platform for mapping disease-associated brain circuitry and advancing the clinical efficacy of DBS.

10:30-11:30 **Keynote Speaker.** Closing the translational gap between mutant mouse models and the clinical reality of psychotic illness. J. L. Waddington

Closing the translational gap between mutant mouse models and the clinical reality of psychotic illness. John L. Waddington, Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland. As animal models of psychotic illness become more refined, mutant mouse models have become increasingly prominent through their ability to inform on the structural, cellular and behavioural roles of genes associated with risk for psychosis via the phenotypic consequences of disruption of those genes. This presentation will consider recent advances in the field whereby mutant mouse models seek to reflect increasing knowledge of psychotic illness, focusing on four main themes: 1. That psychosis is disrespectful to conventional diagnostic boundaries, both clinically and in terms of pathobiology: it extends beyond schizophrenia to include several diagnostic categories and may be best captured in terms of psychopathological dimensions rather than/additional to such categories. 2. That a given risk gene (G) does not operate in isolation but, rather, appears to participate in complex interactions with environmental (E) risk factors, i.e. G × E interactions. 3. That a given risk gene does not operate in isolation but, rather, is likely to participate in complex, epistatic interactions with other risk genes, i.e. G × G interactions. 4. That 'hard' biological indices of developmental perturbation(s) over early fetal life, such as minor physical anomalies and craniofacial dysmorphology, can be evaluated mechanistically via mutant mouse models in a manner that is conceptually and technically homologous to how they are evaluated clinically. Such studies constitute important steps in closing the translational gap between mutant mouse models and the clinical reality of psychotic illness. The author's studies are supported by Science Foundation Ireland and the Wellcome Trust.

1:00-2:45 **Oral Session 2. Disease**

Effects of Antalarmin on hippocampal pCREB expression and characterisation of sociability and social memory in male rats following global cerebral ischemia. Patricia B. de la Tremblaye, Nicolas Narvaez Linares & Hélène Plamondon, Ph.D. Changes in emotionality reported following stroke can affect sociability through distinct changes in brain processes. CRH type 1 receptors (CRHR1) have been implicated in social behavior via its effects on anxiety. CRHR1 also play a modulatory role on expression of cAMP-response element-binding protein (CREB), an activity-dependent gene transcription factor required for the formation of memory in several hippocampus-dependent cognitive tasks, including social recognition. At present, little is known about the function of CRHR1 signaling in social interaction and memory, and its physiological role in the modulation of hippocampal pCREB activity following vascular brain injury. Thus, the current study aims to characterize the effects of global cerebral ischemia on social behaviour & on pCREB expression in the hippocampus, and to determine effects of an acute pre-ischemic treatment with the CRHR1 antagonist Antalarmin on these variables. Adult male Wistar rats (N =50) were exposed to 10 minute global cerebral ischemia or sham operation, which was induced by four vessel occlusion (4VO). Antalarmin (ANT; 2μg/μl) or saline was icv injected 30 min before 4VO. On the 8th day following reperfusion, rats were subjected to the Three Chamber Social Approach Test to measure sociability and preference for social novelty. Thirty days after ischemia, the expression of pCREB was detected by fluorescence immunostaining and analysed using Image J. Our findings support enhanced sociability and preference for social novelty in saline-treated ischemic compared to sham rats. This appears partly related to changes in anxiety levels, considering that ANT enhanced sociability in sham rats. Interestingly, ANT-treated ischemic rats showed similar behaviour as the saline-treated sham rats. We are characterizing the impact of ANT on neuronal preservation, a phenomenon that could contribute to observed effects. Thirty days post ischemia, immunochemical detection revealed long-lasting and injury specific increases in pCREB-expressing cells in the CA1 region of the hippocampus, a phenomenon that was significantly attenuated by ANT treatment. It is unlikely that neuronal expression alone be accountable for such changes as CA1 neurons are most vulnerable to ischemic damage. Conversely, glial cells are known to proliferate after ischemia, also express pCREB and may be involved, a possibility that we are investigating.

Npas4 regulates vulnerability to stress during adolescence. Coutellier, L. Ohio State University. Specific windows of postnatal brain development are known to be particularly involved in the risk of developing mental illnesses in adulthood. Adolescence is such a window during which environmental stress can have long lasting consequences on social and cognitive functions. In individuals highly vulnerable to stress, relatively mild stressful situation can trigger the onset of psychiatric conditions such as schizophrenia and depression. The mechanisms underlying vulnerability to stress are not well understood. Identifying these mechanisms can help to understand the etiology of some of the psychiatric conditions triggered by environmental stress. Here we show that the brain specific transcription factor Npas4 could regulate vulnerability to stress during adolescence. We first determined Npas4 expression level in the cortex of C57Bl/6 mice at different ages using western blot. We observed that Npas4 is highly expressed in the adolescent brain when compared to aged mice. We then used Npas4 heterozygotes (HET) and wild-type (WT) to determine whether low level of Npas4 in the brain during adolescence affects sensitivity to stress. WT and HET mice were exposed to chronic mild stress during adolescence (from 4 to 6 weeks old) or kept in standard rearing conditions (control). Prefrontal-cortex dependent memory was assessed in adulthood (12 weeks old) using the spontaneous alternation test and object/context mismatch test. We observed that WT mice were not affected by the chronic mild stress situation and have normal cognitive function in adulthood. However, adult HET mice exposed to chronic mild stress during adolescence display severe cognitive deficits, while they have only moderate impairments deficits when raised in standard conditions. These findings suggest the importance of Npas4 during adolescence, a period of high neuronal plasticity and of extreme sensitivity to environmental stimuli. In addition, our preliminary findings indicate that Npas4 could regulate stress vulnerability during adolescence by controlling postnatal neurogenesis.

External Auditory Perception and Auditory Hallucinations in Schizophrenia. Toshikazu Ikuta (University of MIssisippi), Pamela DeRosse, Katherine H Karlsgodt, Philip R. Szeszko, Anil K. Malhotra (Zucker Hillside Hospital). The impact of auditory hallucinations on neural activity during external auditory perception when hearing existing sounds is not well understood. While cortical regions important for language have been implicated during auditory hallucinations, subcortical structures that may be affected by illnesses such as schizophrenia have been associated with auditory perception of speech. In particular, the globus pallidus has been shown to be involved in speech articulation (Wise et al., 1999). We hypothesized that neural activity in sub-cortical structures during external auditory perception would be disrupted in patients with auditory hallucinations. More specifically, we tested the perception of subvocal processes (Wise et al., 1999) when patients hear a human voice in relation to a non-human voice sound. Sixteen patients diagnosed with schizophrenia participated in the study. During the fMRI session, auditory stimuli were presented in one-second intervals at times when scanner noise was absent. Participants listened to auditory stimuli of sine waves (SW) (4kHz-5.5kHz), English words (EW), and acoustically reversed English words (rEW) in a block design fashion. rEW were employed to deliver the sound of a human voice with minimal linguistic components. Patients' auditory hallucination severity was assessed by the auditory hallucination component of the Brief Psychiatric Rating Scale (BPRS). We found bilateral activation of the globus pallidus during perception of rEW when compared with perception of SW. This activation in left globus pallidus correlated with severity of auditory hallucinations. EW when compared with rEW did not correlate with auditory hallucination severity. The correlation did not appear to be affected by medication type. Our findings suggest that subcortical structures implicated in schizophrenia are sensitive to the perception of subvocal processes without linguistic elements. This relationship is affected by severity of auditory hallucinations.

Preclinical evaluation of the fast acting antidepressant potential of dextromethorphan: involvement of AMPA and sigma receptors. Matsumoto, R. and Nguyen, L. West Virginia University, Morgantown, WV. The ability of subanesthetic doses of ketamine to produce rapid and robust antidepressant effects in humans overcomes a major limitation of current antidepressant medications, namely the delayed onset of therapeutic response. However, the widespread use of ketamine remains limited by its adverse effects and abuse potential. Thus, in the present preclinical study, the over-the-counter antitussive dextromethorphan was investigated as a potential alternative to ketamine due to its overlapping pharmacodynamic properties. In addition, the involvement of AMPA and sigma receptors in the antidepressant-like effects of dextromethorphan was investigated because accumulating evidence suggests that these mechanisms contribute to a fast onset of antidepressant efficacy. Administration of dextromethorphan to male, Swiss Webster mice significantly and dose dependently reduced immobility time in the forced swim test ($P<0.001$) and tail suspension test ($P<0.001$), similar to the positive controls for fast acting and conventional antidepressant effects characterized by ketamine and imipramine. Using the forced swim test, the most validated model for predicting antidepressant efficacy, pretreatment of mice with a dose of NBQX (AMPA antagonist) or BD1063 (sigma antagonist) that alone had no significant effects, attenuated the antidepressant-like actions of dextromethorphan, confirming the involvement of both AMPA ($P<0.01$) and sigma ($P<0.05$) receptors in these effects. Of note, there was no correlation between the behaviors of the animals in the forced swim test (or tail suspension test) with locomotor activity in an open field, confirming that the antidepressant-like effects of dextromethorphan were independent of stimulant effects. Although dextrorphan, a major metabolite of dextromethorphan, also reduced immobility time in the forced swim test ($P<0.005$), these effects were not altered by pretreatment with AMPA or sigma receptor antagonists (n.s.). Moreover, addition of the CYP2D6 inhibitor quinidine to dextromethorphan potentiated the antidepressant-like effects of dextromethorphan ($P<0.005$), which together with the dextrorphan data, indicate that the antidepressant-like effects of dextromethorphan are not dependent on the formation of major metabolites. Together, the data show that dextromethorphan exerts antidepressant-like effects through AMPA and sigma receptors, and additional studies are warranted to further investigate its fast acting antidepressant potential.

Beneficial effects of intranasal NPY and HS014 in preventing PTSD related symptomology: Comparative study. Sabban, E. New York Medical College, Valhalla, NY, Serova, L. New York Medical College, Laukova, M, New York Medical College, Alaluf, L., New York Medical College. Single prolonged stress (SPS) animal model of PTSD elicits many of the behavioral impairments associated with PTSD or co-morbid disorders. We recently showed that neuropeptide Y (NPY) and melanocortin receptor 4 antagonist (HS014) when delivered to the brain by intranasal infusion shortly before SPS stressors prevented development of several behavior abnormalities elicited by traumatic stress (Serova et al, 2013, Neurosci. 236: 298-312; Behav. Brain Res. 250: 139-147). Both treatments (NPY and HS014 given in 2 doses) had beneficial effects on anxiety index and many parameters of anxiety-like behavior measured on EPM a week or more afterwards. However, the effects on time spent in open and closed arm was more pronounced in rats with HS014. The depressive-like symptoms (immobility with forced swim) was only reduced with the high dose of HS014 and low dose was ineffective. Response to novel stress was estimated by grooming behavior in the EPM, since it can be induced by stress, and is regulated by ACTH. The high, but not low, dose of HS014 reduced duration of a single bout of grooming. In contrast, IN NPY did not alter grooming behavior on the EPM. Elevated glucocorticoid receptor (GR) levels in the hippocampus is proposed to mediate long-term changes in PTSD patients. Indeed we found that 7 days after SPS stressors, GR levels in the ventral hippocampus are elevated over unstressed controls in animals with IN vehicle, but not NPY. Likewise both concentrations of HS014 prevented the SPS triggered rise in GR in the ventral hippocampus, which may be associated with their effect on anxiety. The effect of IN HS014 on the SPS elicited changes in the HPA axis differed from that of NPY. SPS elicited rise in plasma corticosterone and ACTH were lower after 30 min in rats given IN NPY, compared to vehicle. In contrast, low dose of HS014 did not alter the rise in corticosterone and there was a small, but significant, reduction only with the high dose. Neither dose of HS014 prevented the elevation of plasma ACTH. Overall, the results reveal differences in ability of IN NPY, as well as widely divergent doses of MCR4 antagonist, to modulate behavioral and molecular responses to traumatic stress in a PTSD animal model.

Extracellular signal-regulated kinase-2 regulates adult functional responsivity to stressful situations induced by Prozac exposure during adolescence. Iñiguez, S. California State University San Bernardino; Riggs, L. California State University San Bernardino; Nieto, S. California State University San Bernardino; Dayrit, G. California State University San Bernardino; Warren, B. Florida State University; Nestler, E. Mount Sinai School of Medicine; Bolaños-Guzman, C. Florida State University. The neurobiological mechanism(s) underlying the enduring consequences of antidepressant exposure during adolescence are poorly understood. Here, we assessed the long-term effects of exposure to fluoxetine (FLX), a selective serotonin reuptake inhibitor, during adolescence on behavioral reactivity to emotion-eliciting stimuli. We administered FLX (10 mg/kg, twice daily, for 15 days) to male adolescent C57BL/6 mice (postnatal day [PD] 35-49), and assessed their reactivity to the social defeat, forced swim test, and elevated plus-maze procedures, 21 days after treatment. We also examined the effects of FLX treatment on the expression of extracellular signal-regulated kinase 1/2 (ERK) and related signaling within the ventral tegmental area (VTA) of adolescent mice and Sprague-Dawley (PD35-49) rats. Exposure to FLX during adolescence induced a stress-resistant/resilient phenotype as measured in the social defeat and forced swim test, along with enhanced sensitivity to the anxiety-eliciting environment of the elevated plus-maze in adulthood. This paradoxical behavioral phenotype was accompanied by decreases in ERK2 mRNA and protein phosphorylation within the VTA, while stress alone resulted in opposite effects. Pharmacological (U0126) inhibition, as well as virus-mediated downregulation of ERK2 activity within the VTA, mimicked the behavioral profiles observed after juvenile FLX treatment. These findings suggest that FLX exposure during adolescence results in long-lasting decreases in sensitivity to stress, along with increased sensitivity to anxiogenic stimuli, and that this complex behavioral profile may be mediated by adaptations in ERK signaling within the VTA. Together, our results further delineate the role VTA-ERK signaling plays in regulating mood-related behaviors across the lifespan.

Widespread cortical α-ERD companying visual oddball target stimuli is frequency but non-modality specific. Weiwei Peng and Yong Hu, Department of Orthopaedics and Traumatology, The University of Hong Kong, Hong Kong, China;. Objective: Previous findings have shown that alpha event-related desynchronization (α-ERD) is associated with reaction to visual stimuli in oddball paradigm, as a reflection of attention allocation and memory updating. This study tested the hypotheses that it reflects a modality and/or frequency specific mechanism. Methods: EEG recordings (64 channels) were performed on 18 healthy subjects during visual, auditory, somatosensory, and pain oddball paradigms. Low- and high-frequency α rhythms were analyzed on individual basis, and their sources were estimated by low resolution brain electromagnetic tomography (LORETA). α-ERD, served as an index of cortical activation, was computed on the cortical voxel level and compared across the conditions (target vs. non-target), alpha sub-bands (lower vs. higher frequency), and modalities (visual, auditory, somatosensory, and pain). Results: In the visual modality, α-ERD was mainly generated from occipital cortex for both target and non-target conditions. Its magnitude was enhanced across widespread cortical regions (e.g., bilateral occipital, parietal, and frontal areas) in the target condition and was greater in high frequency α band. Finally, α-ERD difference between target and non-target conditions was not higher in visual than that in other control modalities. Conclusions: Human high frequency α-ERD reflects attention processes underlying reaction to oddball target stimuli regardless stimulus modality.

1:00-2:45 **Oral Session 3: Mechanisms**

Insular activation during reward anticipation reflects duration of illness in abstinent pathological gamblers. Tsurumi, K. Department of Psychiatry, Graduate School of Medicine, Kyoto University; Kawada, R. Department of Psychiatry, Graduate School of Medicine, Kyoto University; Yokoyama, N. Department of Psychiatry, Graduate School of Medicine, Kyoto University; Murai, T. Department of Psychiatry, Graduate School of Medicine, Kyoto University; Takahashi, H. Department of Psychiatry, Graduate School of Medicine, Kyoto University. Introduction: Pathological gambling (PG) is a chronic mental disorder. PG patients cannot stop gambling behavior despite negative consequences. Accumulative evidence suggests that PG has many similarities with substance use disorders. However, progression of substance use disorders is known to be affected by drugs of abuse, while how PG develops remains unclear. In addition, although being abstinent from drug of abuse partly recover altered brain structure in substance abusers, how abstinence from gambling behavior affect neural substrate in PG patients. Methods: Twenty-three PG and 27 age and gender matched healthy controls (HC) were studied. Using fMRI, brain activations during reward anticipation was measured with monetary incentive delay task. Results: During reward anticipation, PG showed decreased activity compared with HC in broad range of reward system, including insula, and cingulate cortex. In PG participants, activation in the left insula was negatively correlated with duration of illness, and activation in the left insula showed modest positive correlation with duration of abstinence. Conclusion: During reward anticipation, the longer the duration of illness of PG was, the less the PG patients showed left insula activation, in addition, the longer the abstinence from gambling behavior, the more the PG patients showed left insula activation. Our findings suggest that activation in the insula during reward anticipation may serve as a marker of progression and recovery of PG.

Neural correlates of social interaction during exposure to an acute stressor: companion identity matters. Weinstein, T.A.R. California National Primate Research Center, University of California, Davis; Cherry, S.R. Center for Molecular & Genomic Imaging, University of California, Davis; Bales, K.L. California National Primate Research Center & Department of Psychology, University of California, Davis. Countless studies identify social support as critical in protecting against the deleterious mental and physical health consequences of acute and chronic stress, yet it is unclear which types of social relationships are most beneficial or which neurobiological mechanisms are involved. We examined neural responses to an acute stressor, separation from the natal group, in six 2-year-old rhesus macaques (Macaca mulatta) using positron emission tomography (PET).

Prior to separation, we conducted 15 ten-minute observations per subject to measure affiliative preferences (i.e. friendships). During separation, subjects were either housed alone, with access to a familiar (but not preferred) peer from the natal group through a grate, or with access to a friend through a grate. Subjects experienced each housing condition in a randomly predetermined, counterbalanced order. Twenty four hours after separation, subjects were injected with 1 mCi/kg [F-18]-fluorodeoxyglucose, and then were videotaped for a 30-minute conscious uptake period to record social interactions with the companion. Immediately afterward, subjects were anesthetized and scanned using a microPET P4 primate scanner. PET data were co-registered with structural magnetic resonance images. Preliminary analysis revealed greater glucose uptake in the nucleus accumbens in the "familiar peer" condition as compared to the "alone" condition (GLM Repeated Measures, $p = 0.02$). In addition, nucleus accumbens activity significantly positively correlated with the total time the familiar peer spent in proximity to the grate during the uptake period, as well as the amount of time that the subject and familiar peer simultaneously spent in proximity to the grate (both Spearman's rho = 0.83, $p = 0.04$). No interactions between the subject and friend significantly correlated with nucleus accumbens activity. The nucleus accumbens contains a high density of dopaminergic neurons and responds particularly to unanticipated reward. Our results suggest that interacting with the familiar peer may have been unexpectedly rewarding as compared to interacting with the friend, whose social support in a stressful context might have been anticipated, and a therefore less potent stimulator of the neural circuits mediating reward.

Lesions of the basolateral amygdala induce elevated risk-taking in rats. Orsini, CA; Trotta, R.; Bizon, J.L.; Setlow, B.; University of Florida. Each day, individuals are faced with decisions that require choices among options with potentially adverse consequences. Although most individuals are able to effectively balance rewards and risks so as to make adaptive choices, certain psychiatric conditions like addiction can contribute to biased choice towards overly risky options. The current study focused on elucidating the neural basis of risky decision-making with the long term goal of understanding how this circuitry can become altered by psychiatric disease. The role of the basolateral amygdala (BLA) in some forms of decision-making is relatively well-established, but its specific role in integrating reward and risk-related information during decision-making is less clear. To this end, we assessed the effects of neurotoxic BLA lesions in a rat model of risky decision-making [the Risky Decision-Making Task (RDT)], in which rats choose between a small, "safe" food reward and a large, "risky" food reward that is accompanied by variable probabilities of punishment (mild footshock). Rats (n=33) were trained in the RDT and then received either neurotoxic or sham BLA lesions. Rats were then re-tested on the RDT. Before surgery, there were no differences between sham and lesion groups in choice of the large, risky reward. After surgery, lesioned rats displayed significantly greater choice of the large, risky reward relative to sham rats (increased risk-taking). When reward magnitudes in the RDT were equated (such that rats chose between a small, safe and a small, risky reward), both groups shifted their choice to the non-shock-associated lever, indicating that BLA lesions did not affect rats' sensitivity to punishment. Rats were then given i.p. injections of amphetamine and tested on the RDT. Amphetamine reduced risk-taking, irrespective of lesion condition. Finally, rats were tested for food-reinforced lever pressing on various fixed ratio schedules. There were no significant differences between the 2 groups in their lever pressing, indicating that elevated risk-taking in lesioned rats was not due to an increase in food motivation. Together, these findings show that the BLA is crucial for integrating reward and risk-related information to guide adaptive choice behavior in response to risk of adverse consequences. This shift in risk-taking cannot be accounted for by impaired responsivity to punishment, as both systemic amphetamine and a reduction in the risky reward magnitude decreased risk-taking.

Effect of l-glutamate application in the gut and preoptic area on thermoregulation in rats. Trina Sengupta, Ashok Kumar Jaryal, Hruda Nanda Mallick, All India Institute al Sciences, New Delhi. Aims: L-glutamate is an excitatory neurotransmitter and a constituent of dietary protein. Thermography in rats after intragastric administration of l-glutamate led to brown adipose tissue (BAT) thermogenesis alongwith activation of preoptic area (POA) as revealed from fMRI studies. POA is important for thermoregulation which has glutamatergic receptors. There are studies in anesthetized rats showing varying temperature changes after intrapreoptic

microinjection of l-glutamate. However changes in body, brain and BAT temperature (Tb, Tbr and TBAT) in unrestrained rats after intrapreoptic and intragastric administration of l-glutamate is lacking. Methods: Study was divided into two groups. Tbr, TBAT was recorded with a K-type thermocouple placed near hypothalamus and BAT respectively and Tb was recorded by a peritoneal transmitter. 20 rats of 1stgroup were divided into two sub-groups. Group Ia rats were microinjected with kynunerate (KYNA, 0.11nM) followed by l-glutamate (0.14nM) via a implanted guide cannula at the POA and the group Ib was microinjected with l-glutamate. In group II effect of intragastric administration of glutamate (0.12mM) and NaCl (0.12mM) on temperature in 10 rats was performed. Temperature was recorded for 6 h. Results: Long-lasting increase in temperature by l-glutamate microinjection in the POA was attenuated by KYNA injection prior to l-glutamate. Short but instantaneous rise in TBAT along with slow rise in Tb and Tbr was observed in the l-glutamate administered rats; while no increase was observed after NaCl administration. Conclusion: Preoptic ionotropic glutamatergic receptors induce hyperthermia and dietary l-glutamate leads to BAT thermogenesis.

Enhanced performance in GluA1 knockout mouse in the 5-CSRTT. Tomasz Schneider, David Bannerman, Nuffield Department of Clinical Neurosciences, University of Oxford, JR Hospital, Oxford OX3 9DU. In the absence of subunit-specific pharmacological tools, insight into the contribution of specific AMPA receptor subunits to various behavioral processes has come from studies of mutant mice with targeted subunit deletions. GluA1 'knockout' (KO) mice have impaired synaptic plasticity and display a complex pattern of behavioural abnormalities relevant to schizophrenia (e.g., novelty-induced hyperactivity, impaired prepulse inhibition) and depression (e.g., behavioral 'despair' after repeated stress, less social interactions). GluA1 KO show also impaired spatial working/short-term memory, but intact associative, long-term spatial reference memory suggesting a deficit in short-term habituation. Here we present the results of the 5-Choice Serial Reaction Time Task (5-CSRTT) performance in two different cohorts of GluA1 KO mice. Training begun with response holes illuminated for 16 s (stimulus duration, SD), followed by the introduction of progressively more demanding task parameters down to 0.5 s SD. GluA1 KO mice showed overall better performance in this test with smaller number of omissions, higher number of rewards earned, and better accuracy; however, KO mice displayed a very specific pattern of task acquisition. GluA1 mice showed more anticipations (increased impulsivity) during initial training (16 s SD) and when the task demands increased (transition from 1 to 0.5 s SD) and they responded more in total due to increased number of correct responses. This was not mediated by hyperactivity as the latencies to correct/incorrect responses and to magazine did not differ between the groups. GluA1 KO mice also showed a better reacquisition of the task after cessation of training, but similar to control mice drop in performance under pre-feeding condition and after introduction of a distractor (flashing light) used to manipulate motivation and attentional span, respectively. We suggest that a deficit in short-term habituation that we previously reported in GluA1 KO mice might be responsible for their better performance in the 5-CSRTT; however, this 'sticky attention' may also have negative consequences when it comes to extinction of drug-seeking or not-any-longer relevant conditioned reinforcement, both of which were reported in GluA1 KO mice previously. Although these mice, like any other single mutant line, are unlikely to model the entire disease, they may provide a useful tool for studying the role of GluA1 in the pathophysiology of major psychotic illness.

Eating, drinking and sleeping: the role of 5-HT1A receptor in the serotonin-mediated dipsogenic and hypnogenic responses in pigeons (Columba lívia). Dos Santos, TS. Department of Physiological Sciences, CCB, Federal University of Santa Catarina, 88040-900, Florianópolis SC, Brazil. Krueger, J. Department of Physiological Sciences, CCB, Federal University of Santa Catarina, 88040-900, Florianópolis SC, Brazil. Melleu, FF. Department of Physiological Sciences, CCB, Federal University of Santa Catarina, 88040-900, Florianópolis SC, Brazil. Poli, A. Department of Pharmacological Sciences, CCB, Federal University of Santa Catarina, 88040-900, Florianópolis SC, Brazil. Herold, C. C. & O. Vogt-Institute for Brain Research, Heinrich-Heine-University,40225, Düsseldorf, Germany. Güntürkün, O. Institute for Cognitive Neuroscience, Faculty of Psychology, Ruhr-University, Bochum, 44780, Bochum, Germany. Marino-Neto, J. Department of Physiological Sciences, CCB, Federal University of Santa Catarina, 88040-900, Florianópolis SC, Brazil.

Institute of Biomedical Engineering, EEL-CTC, Federal University of Santa Catarina, 88040-900 Florianópolis SC, Brazil. Introduction: serotonergic circuits inhibit ingestive and sleep behaviors both in mammals and birds. Intracerebroventricular (ICV) serotonin (5-HT) injection in pigeons, however, increases water intake and sleep. 5-HT1A receptor (5-HT1AR) activation causes similar responses. However, the 5-HT1AR can act as auto as well as heteroreceptor, and produces different effects based on its location. Therefore, this study investigated the role of 5-HT1AR on dipsogenic and hypnogenic 5-HT-mediated responses. Methods: adult naïve pigeons (both sex, 400-550g) were injected ICV with 5-HT (150 nmol), 8-OH-DPAT (DPAT, 30 nmol), 20 min. after pretreatment with WAY100635 (WAY, 5-HT1A auto/heteroreceptor antag., N: 8) or MM77 (heteroreceptor antag., N: 8). Behavioral analysis were took during one hour and the food and water intake was evaluated at the end of this period. Additional 12 pigeons received bilateral ICV injection of the serotonergic neurotoxin 5,7-Dihydroxytryptamine (5,7-DHT, 200µg/injection; N:6) or vehicle (N:6). Past 12 days tests with 5-HT or DPAT started. The animals were killed 28 days after the surgery and the hypothalamic levels of 5-HT were analyzed. Another 2 groups of 5,7-DHT (N: 6) or vehicle (N:6) injected pigeons were perfused on the 12th day to verify 5,7-DHT effects on 5-HT neurons. Additionally, we evaluated Fos protein expression in hypothalamic nuclei with high density of binding sites to the radioligand [3H] 8-OH-DPAT, after ICV injection of 5-HT (N:5), DPAT (N:5) or vehicle (N:5). 90 min. later, the animals were perfused and hypothalamic sections reacted to detect Fos protein. Results: both 5-HT and DPAT increased drinking and sleep. These effects were partially or totally inhibited by the antagonists. 5,7-DHT decreased 5-HT levels and serotonergic neurons density, however, did not affect the treatment-mediated behavioral changes. The treatments also increased Fos protein activation in hypothalamic regions with high 5-HT1A receptors density that seem to be involved with food, body fluid and sleep regulation. Conclusion: the behavioral responses evoked by 5-HT seem to be mediated by both 5-HT1AR. The heteroreceptors are probably situated on key hypothalamic regions involved with ingestive and sleep/wake cycle regulation in birds. Our results also indicate small differences in the neuronal activity evoked by 5-HT and DPAT suggesting that other serotonergic receptors also contribute to the 5-HT role on ingestive and sleep control. Support: CNPq

Lesions of Area 8 impair visual conditional selection but not monitoring in working memory. Michael Petrides, Montreal Neurological Institute, McGill University, 3801 University Street, Montreal, Quebec H3A 2B4, Canada. In the primate brain, the posterior part of the lateral frontal cortex consists of the agranular motor and premotor cortex. Anterior to this agranular premotor-motor cortical region lies the enormously expanded lateral prefrontal cortex. The posterior part of the lateral prefrontal cortex that lies immediately in front of the premotor region is area 8, a highly granular prefrontal area that has been shown to be critical for attentional control and for the selection of visual and auditory stimuli in the environment based on conditional if-then rules. In the present study, monkeys with lesions to area 8 were tested on a monitoring working memory task in which they were required to track (monitor) their own choices from a display of three objects. The latter task is known to be sensitive to lesions of the mid-dorsolateral prefrontal cortex (areas 46 and 9/46). The monkeys with area 8 lesions were not impaired in performing the monitoring working memory task, although they were severely impaired in learning visual conditional associative tasks in which they were required to select one of two objects depending on the visual instruction cue that was presented. These findings add further support to the functional dissociation that exists between the posterior dorsolateral prefrontal region (area 8) that is involved in the selection of objects in the environment based on learned rules and the more anteriorly located mid-dorsolateral prefrontal cortex (areas 46 and 9/46) that is critical for the monitoring of information in working memory. The posterior dorsolateral area 8 receives input from visual and auditory sensory association areas and is in a position to regulate attentional focus within these areas via long efferent axons. These anatomical connections are probably the basis of a frontal system for regulating the attentional selection of objects in the environment. By contrast, the mid-dorsolateral prefrontal region which is linked to posterior cingulate and retrosplenial cortex is in a position to track information in working memory.

3:30-5:30 **Symposia: Neural mechanism of regulation and disruption of motivational behaviors.**
Chairs: Hidehiko Takahashi, Christelle Baunez

Ventral Striatal Contributions to Performance Under Pressure. Vikram S. Chib. Department of Biomedical Engineering, Johns Hopkins School of Medicine; Kennedy Krieger Institute. It is widely assumed that large financial incentives will increase a worker's motivation, which, in turn, will elicit improved behavioral performance. However, recent behavioral experiments suggest a more idiosyncratic interplay between incentives and performance: when executing skilled tasks, an individual's performance increases as the level of incentive increases only up to a point, after which greater incentives paradoxically decrease performance. Despite the ubiquity of performance-based incentive schemes, the neural and psychological underpinnings of the relationship between incentives and performance are not well understood. In this talk I will present functional brain imaging data that was obtained while subjects performed a skilled motor task for varying levels of monetary incentive. We found that ventral striatal signals during the motor task were predictive of subjects' performance decrements for large incentives. Furthermore, an independent measure of subjects' preferences for avoiding losses as compared to equal magnitude gains (i.e., loss aversion) was predictive of striatal responses and behavioral decrements. These results are indicative of a neural mechanism underlying 'choking' when the stakes are high: the ventral striatum encodes the prospect of losing an incentive at the time of task performance, and the severity of this loss aversion induces performance decrements. Finally, I will show how accounting for a subject's loss aversion during incentive mechanism design can ameliorate performance decrements for large incentives. These findings illustrate how the field of neuroeconomics can inform neuropsychological and economic theories, and have practical applications for the improvement of performance and productivity in daily life.

Molecular neuroimaging on risk assesment: Beyond dopamine. Hidehiko Takahashi, Kyoto University Graduate School of Medicine, Japan. Over the last decade, an interdisciplinary field of research, known as neuroeconomics, has begun to flourish. Neuroeconomics represents the integration of economics and neuroscience, and explores patterns of decision-making by adopting neuroimaging methods, including functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). A primary goal of neuroeconomics research is to reveal the neural basis of "irrational" or "emotional" decision-making, and the role of reward system (e.g. striatum, dopamine). A subsequent research question involves exploring the modulatory role of neurotransmission in these central processes. I will talk about our positron emission studies (PET) and pharmacological studies investigating the neurochemical basis of "irrational" decision-making under risks beyond dopamine.

The monoamine system in monetary incentives. Makiko Yamada. Dopamine and norepinephrine are monoamine neurotransmitters, which have been implicated in the regulation of motivational behaviour for efficient decision-making. In order to clarify the association between these neurotransmitters and neural responses to decision process, we measured brain activity during a monetary incentive delay task using functional magnetic resonance imaging, and dopamine D2 receptors and norepinephrine transporter using positron emission tomography with [11C]raclopride and (S,S)-[18F]FMeNER-D2. The role of monoamine system in monetary incentives is discussed.

The role of the subthalamic nucleus in impulse control disorders. Christelle Baunez, Institut de Neurosciences de la Timone, UMR7289, CNRS & Aix-Marseille University, Marseille, France. The subthalamic nucleus (STN) is known for its involvement in neurological disorders such as Parkinson's Disease, as it is the target for deep brain stimulation (DBS) in this disease. The involvement of STN in non-motor processes has also been demonstrated and led to target it for the treatment of obsessive compulsive disorders. In this context, we have previously shown that STN is a major component of a network controlling inhibitory processes. We have assessed the effects of STN lesions or DBS in decision making, in gambling, but also in another disease related to loss of impulse control : addiction. We suggest STN to be an appropriate target for application of DBS as a treatment for addiction.

3:30-5:30 **Symposia: Scents that matter – from olfactory stimuli to genes, behaviors and beyond**.
Chairs: M. Fendt, Y. Kiyokawa

A juvenile mouse pheromone controls adult social behavior. Liberles, S. Harvard Medical School. The mouse olfactory system provides a powerful model for understanding innate behavior. Mouse pheromones are chemical signals that provide social information about sex, status, and age, and evoke complex behavioral and endocrine responses in other individuals of the same species1. Olfactory cues, including pheromones and predator odors, can elicit or inhibit sex, aggression, fear, and parental care. However, little is understood about how particular odors and pheromones are processed by neural circuits to cause specific behavioral responses. We recently identified a novel pheromone produced in the tears of young, juvenile mice (2-3 weeks of age) that functions to inhibit sexual responses in adult animals2. This pheromone, exocrine gland-secreting peptide 22 (ESP22), activates highly tuned sensory neurons in the vomeronasal organ (VNO), and a neural pathway that involves the medial amygdala. Knockout mice that lack VNO function fail to respond to ESP22, and display increased sexual behavior towards prepubescent animals. Understanding the neurons responsive to ESP22 in the periphery and brain, and how these differ in form and function from other neurons in the vomeronasal pathway that respond to sex pheromones and predator odors, will provide a foundation for dissecting molecular mechanisms underlying odor-driven behaviors. 1 Liberles, S. D. Mammalian pheromones. Annu Rev Physiol 76, 151-175, (2014). 2 Ferrero, D. M. et al. A juvenile mouse pheromone inhibits sexual behaviour through the vomeronasal system. Nature 502, 368-371, (2013).

An alarm pheromone in rats. Kiyokawa, Y. Laboratory of Veterinary Ethology, The University of Tokyo; Inagaki, H. Laboratory of Veterinary Ethology, The University of Tokyo; Takeuchi, Y. Laboratory of Veterinary Ethology, The University of Tokyo; Mori, Y. Laboratory of Veterinary Ethology, The University of Tokyo. Animals release specific biochemicals when exposed to stresses, possibly to warn or alarm the nearby conspecifics; some of these biochemicals are called an alarm pheromone. In this study, we assessed an alarm pheromone in the male rats. Two pheromone-donor male rats were placed in a box and were exposed to foot shocks, after which they were removed and a pheromone-recipient male rat replaced them in the box. Pheromone-recipient male rats showed a significant rise in their body temperature. This finding suggests that the pheromone-donor rats released an alarm pheromone on receiving foot shocks. Subsequently, we found that the alarm pheromone was released from the perianal region of the pheromone-donor rats. We established a technique to trap the released pheromone in water and measure the effects of pheromone exposure on pheromone-recipient rats in diverse experimental models by placing filter papers soaked with pheromone-containing water. The presence of the alarm pheromone increased the anxiety level in pheromone-recipient rats through the vomeronasal system, resulting in an increased body temperature in their home cage, increased defensive and risk assessment behaviors in a modified open-field test, deteriorated male sexual behavior, and enhanced acoustic startle reflex (ASR). Because the alarm pheromone was found to be volatile, we collected and fractionated all the volatile chemicals released from the perianal region of pheromone-donor rats. Considering the fractions positive for pheromone activity when they enhanced the ASR, we successively fractionated the positive fractions until they yielded two candidate pheromone molecules. When the rats were exposed to a mixture of and individually to the two molecules, only their mixture enhanced the ASR. Therefore, we deduced that the binary mixture constituted an alarm pheromone in the male rats.

Detection and internal representation of Mup proteins and other predator-derived odors by the vomeronasal system in mice. Papes, F. State University of Campinas; Carvalho, V. State University of Campinas; Nakahara, T. State University of Campinas; Souza, M. State University of Campinas. The nervous system is able to detect, internally represent and process sensory information to generate appropriate behaviors. In mammals, the olfactory sensory system is specialized in the detection of chemical cues, some of which can induce adaptive behaviors critical for the survival of the individual and the species, such as fear, aggression and mating. However, little is known about the molecular nature of most behavior-inducing odors, the sensing olfactory receptors, and the neural processing circuitries to generate appropriate behavioral and endocrine responses. Here, we will present the characterization of several predator-derived odors, including Mup proteins, and their detecting neurons in the vomeronasal organ of mice. We will also present data on the representation of such stimuli in the olfactory bulb, the first processing station of olfactory information in the brain.

Neural correlates of carnivore urine-induced fear. Fendt, M. Institute for Pharmacology and Toxicology & Center for Behavioral Brain Sciences, Otto-von-Guericke-University, Magdeburg, Germany; Wernecke, K. Institute for Pharmacology and Toxicology & Center for Behavioral Brain Sciences, Otto-von-Guericke-University, Magdeburg, Germany; Vincenz, D. Leibniz Institute for Neurobiology & Center for Behavioral Brain Sciences, Otto-von-Guericke-University, Magdeburg, Germany; Storsberg, S. Institute for Anatomy & Center for Behavioral Brain Sciences, Otto-von-Guericke-University, Magdeburg, Germany; D'Hanis, W. Institute for Anatomy & Center for Behavioral Brain Sciences, Otto-von-Guericke-University, Magdeburg, Germany; Goldschmidt, J. Leibniz Institute for Neurobiology & Center for Behavioral Brain Sciences, Otto-von-Guericke-University, Magdeburg, Germany. Defensive behavior induced by exposure to carnivore odor is a well-known paradigm to study innate fear behavior in rodents. In our studies, we are using urine samples of carnivores or 2-phenylethylamine (PEA), a molecule enriched in carnivore urine, to induce avoidance and risk-assessment behavior in Sprague-Dawley rats. PEA is selectively detected by the olfactory receptor TAAR4 (trace-amine associated receptor, subtype 4) and is required for full avoidance behavior against carnivore urine. Using in vivo single-photon emission computed tomography (SPECT) imaging of regional cerebral blood flow, we identified several brain regions which are activated or inhibited by exposure to carnivore urine. This

includes parts of the cingulate cortex, piriform cortex, habenula, interpeduncular nucleus, posterior cortical amygdala, periaqueductal gray, and raphe nucleus. To study the behavioral relevance of these brain areas, we started to temporally inactivate them by local muscimol injections. Such injections into the posterior amygdala, for example, blocked avoidance behavior against carnivore urine. Further studies are focused on how the identified brain areas are connected to each other and how they interact.

5:30-7:30 Poster Session 3

78. **Development of tolerance to ethanol and pentobarbital by the Myers' high ethanol preferring (mHEP) rat allowed to freely consume solutions of ethanol.** B. A. McMillen, S. N. Barry, Z. A. Cormier, S. L. Hendricks, E. N. Shirley and H. L. Williams Department of Pharmacology & Toxicology, Brody School of Medicine at East Carolina University, Greenville, NC 27834 USA. The mHEP rat consumes large quantities of solutions of ethanol in a volitional drinking model. The consumatory period occurs for about 4 hrs after lights-out. When adapted to a two-hour presentation of ethanol solutions, most of the rats obtained BACs greater than 0.08 g/dL (Myers et al, Alcohol 16:343, 1998). Yet, it is difficult to demonstrate that with volitional consumption of ethanol that these rats or other high drinking lines develop adaptive changes and exhibit tolerance. As a further test, mHEP rats from the F35 and F37 generations were screened in a 10-day step-up procedure of 3% to 30% v/v ethanol vs. tap water and then allowed to consume their preferred concentration of ethanol solution or water only as a control. The rats were trained to walk on a rotating rod (12 revs/min) for 60 sec. After at least two weeks of free drinking (Ethanol-treated and pentobarbital-treated rats consumed 5.94±0.70 and 6.01±0.72 g/kg/day during the 3 days prior to testing), either 1.5 g/kg ethanol, 2.0 g/kg ethanol or 15 mg/kg pentobarbital were injected i.p. and at 15 min intervals the rats were placed on the Rotorod and rectal temperature recorded. After 1.5 g/kg of ethanol, the ethanol-drinking rats exhibited a small decrease in ability to walk the Rotorod at 15 min and then returned to baseline of 60 sec for all rats. The control rats exhibited a greater decline in time on the Rotorod at 15 min (10 sec vs. 37 sec). All of the rats were severely impaired 15 min after the 2.0 g/kg dose and showed similar recovery over 60 min. The dose of 15 mg/kg pentobarbital produced a similar pattern in both groups of rats with a severe deficit at 15 min. The 1.5 g/kg dose of ethanol did not alter the rectal temperature and there was a slight rise after pentobarbital of the drinking animals, but the water-only controls exhibited a 1.0° C decrease in temperature from 30 min to 60 min and a 0.8° drop after pentobarbital. The 2.0 g/kg ethanol dose produced a 1.0° to 1.8° drop in body temperature in all rats by 30 min. These data suggest a small degree of tolerance to ethanol had developed due to the consumption of ethanol. In 24 hr access models, the rat will have a high BAC during the dark period, but will not have a measurable BAC by noon (Strickland & Wooles, Alcohol 6:109, 1989). This episodic pattern may limit the development of tolerance due to the low BACs during the lights-on period. (SLH participated in the High School Medicine Research Program)

79. **Early methylphenidate exposure alters morphine-mediated antinociception in neonatal 6-OHDA lesioned female rats.** Kaplan, Graham J, Valentine, Joseph M, Celmer, Jennifer, Crawford, Cynthia A, California State University, San Bernardino. Preclinical data show that treatment with methylphenidate (MPH) during the preweanling period can increase drug intake and alter opioid receptor sensitivity. The relevance of these changes after early MPH exposure to humans treated for ADHD is unclear as these rodents studies were done in "normal" subjects. While the etiology of ADHD is unknown evidence indicates that a deficit in cortical and striatal dopamine system functioning may be responsible for the primary symptoms of this disorder. It is possible that this underlying dysregulation in dopaminergic functioning may cause MPH to have substantially different effects in ADHD patients, when compared to control subjects. Thus, MPH may restore the dopaminergic system to normalcy without causing additional alterations in neuronal functioning. To test hypothesis, we used an animal model of ADHD: the neonatal 6-hydroxydopamine (6-OHDA) brain lesion and assessed the effects of morphine on nociception in adult rats pre-exposed to MPH. Male and female rats were lesioned with 6-OHDA on postnatal day (PD) 3 and given MPH (0, 2, or 5 mg/kg, ip) for 10 consecutive days starting on PD 11. Locomotor activity was assessed during the MPH administration period to determine if the 6-OHDA lesion produced the hyperactive ADHD phenotype. On PD 60, morphine-induced antinociception was assessed using a tail-flick apparatus. Rats were given three baseline trials followed by an injection of

morphine (0, 2.5, 5, 10, or 20 mg/kg, sc). Rats were then tested three additional times with a 20-min intertrial interval. Rats in the lesioned group treated with saline displayed greater amounts of locomotor activity than similarly treated controls on the first day of MPH treatment and lesioned rats had greater levels of locomotor activity regardless of MPH treatment over the entire MPH exposure period. As expected, morphine increased tail-flick latencies however this effect varied according to sex, lesion, and pretreatment condition. Specifically, female rats had significantly greater baseline tail-flick latencies than similarly treated male rats. Overall, pretreatment with MPH (5 mg/kg) decreased tail-flick latencies. However, in female lesioned rats, treatment with MPH (5 mg/kg) increased tail-flick latencies. These data suggest that MPH has the ability to alter opioid receptor sensitivity in an ADHD-like nervous system and could potentially alter the long-term drug use liability in children treated with MPH.

80. **Dietary Supplementations as neuroprotective therapies in a rotenone model of Parkinson's disease in mice.** Islam Zaki, Mohamed Salama, Mohamed El-gamal, Yassmin Youssef, Hoda El-Gamal, Hadeer Osama, Mohamed Sobh, Affiliation: Medical Experimental Research Center (MERC)-Mansoura University. Parkinson disease (PD) is one of most common neurodegenerative disorder characterized by dopaminergic neuronal cell loss in the substantia nigra pars compacta (SNc). The etiopathogenic mechanisms of PD include inflammation, oxidative stress, apoptosis and aberrant cell cycle activation. A long history of PD therapies, all of them consider symptomatic with no actual effects on pathological progression. Rotenone is a naturally occurring pesticide and mitochondrial complex I inhibitor. Chronic systemic exposure to rotenone reproduces many features of PD. Ginkgo leaf extract has shown beneficial effects in treating neurodegenerative diseases like Alzheimer's, cardiovascular diseases, cancer, stress, memory loss, tinnitus, and geriatric complaints like vertigo, age-related macular degeneration, and psychiatric disorders like schizophrenia. These multifaceted activities of the Ginkgo leaf extract may work through various mechanisms of action. The suggested mechanisms of the Ginkgo leaf extract are its antioxidant effect, anti-platelet activating factor (Anti-PAF) activity for cardio and cerebral vascular diseases, inhibition of beta amyloid peptide (Aβ) aggregation to reduce Alzheimer's progression, and decreased expression of peripheral benzodiazepine receptor. The aim of this work was to test the protective effects of Ginkgo leaf extract, on rotenone model of PD in mice. Materials and Method: C57BL/6 mice, weighing about 25 grams were divided into 3 equal groups and received the following for 35 days. Group (1): received daily intraperitoneal injections of 0.5% carboxymethyl cellulose (CMC) 3mL/Kg. Group (2): received rotenone suspended in 0.5% CMC intraperitoneally at a dose of 3 mg/kg, daily. Group (3): received the same rotenone regimen plus daily oral Ginkgo leaf extract at a dose of 100 mg/kg. Then they were evaluated regarding locomotors disturbance on days 20 and 35 then sacrificed at the end of treatment period where brains were subjected to immunohistochemistry for anti TH. Result: Preliminary results showed behavioral improvement, suggesting putative role for Ginkgo leaf extract, this data, however, will be confirmed by postmortem tissue analysis immunohistochemical results (ongoing).

81. **Parental Behavior and the Stress Response in New World Monkeys: A comparative Approach.** Kirk, E.1; Eckles, M. 1; Landis, T. 1; Evans, S. 2,3; Lambert, K.G. 1; Bardi, M. 1 Dept. of Psychology, Randolph-Macon College, Ashland VA USA 230051; DuMond Conservancy, Miami, FL2 and Florida International University, Miami, FL3. New World monkeys are the only nonhuman primates in which several species are characterized by an extensive involvement of fathers in the care of offspring. Variation in female reproductive rates, as well as the paternal investment and male mating effort, have been suggested as possible explanations for these differences (Ross & MacLarnon, 2000). Less investigated are the proximate benefits of parent-infant interactions, such as the effect of parental care on the stress response. In the present study we compared two New World monkey species with different mating systems: owl monkeys (Aotus spp.), in which males and females form mating pairs and fathers display continuous care for infants; and squirrel monkeys (Saimiri boliviensis peruviensus), a

comparable sized species where males are not involved in the care for offspring. The main hypothesis was that the stress response of individuals engaging in parental care should be blunted across species irrespectively of their sex and mating system. Excreted metabolites for cortisol and dehydroepiandrosterone (DHEA) were collected in 11 pairs of owl monkeys (5 with reproductive experience, 6 without) and on 12 squirrel monkeys females (6 mother and 8 adult with no offspring). Results indicated that experienced owl monkeys pairs had significantly higher DHEA / cortisol ratios following exposure to a moderate stressor (training session and novel objects introduction). In squirrel monkeys, results revealed that maternal females not only exhibited more energy conserving behaviors than non-maternal females, but also had a higher DHEA/cortisol ratio, indicating once again higher stress resilience. In sum, this research suggests that, in both bi-parental and uni-parental species, parental experience is related adaptive modifications in resilience. Corroborating previous research demonstrating adaptive modifications in emotional responses in reproductively experienced rodents, the current results extend these findings to New World monkey species with different mating systems.

82. **Serotonin in the Ventral Hippocampus Modulates Anxiety-Like Behavior During Amphetamine Withdrawal.** Jamie L. Scholl1, Wenyu Tu1, Ashley Cook1, Mackenzie Mears1, Michael J. Watt1, Kenneth J. Renner2 & Gina L. Forster1 Center for Brain and Behavior Research; 1Basic Biomedical Sciences, Sanford School of Medicine; 2Biology Department; University of South Dakota, Vermillion, SD. Withdrawal from amphetamine is associated with long lasting alterations in anxiety behavior as well as increased sensitivity to stressors in rodent models of addiction. Rats undergoing amphetamine withdrawal fail to exhibit stress-induced increases in serotonin (5-HT) in the ventral hippocampus (VHipp). Serotonin in the hippocampus is important for stress adaptation, and deficits in 5-HT are related to increased anxiety-like behavior. Therefore, we tested the hypothesis that reduced 5-HT in the VHipp increases anxiety during amphetamine withdrawal. First, we tested whether reducing 5-HT in the VHipp directly increases anxiety behavior. Male rats were bilaterally infused with a serotonergic toxin, 5,7-DHT, or vehicle into the VHipp. Two weeks following infusions, rats were tested on the elevated plus maze (EPM) for anxiety-like behavior, and brains were then collected and the selectivity of the lesion was determined with HPLC. We observed a 70-90% reduction in 5-HT within the vHipp, with no significant difference observed between lesioned rats and sham controls in 5HT within the dorsal hippocampus or for other monoamine neurotransmitters in the hippocampus. Locomotion was not affected in the EPM, but reducing vHipp 5-HT significantly decreased the time spent in the open arms of the maze. Next we tested whether increasing 5-HT in the VHipp reverses anxiety behavior exhibited by rats undergoing amphetamine withdrawal. Rats were treated with either amphetamine or saline for 2 weeks and allowed to undergo withdrawal for 2 weeks. Following withdrawal, rats were infused with paroxetine or vehicle bilaterally into the vHipp and then tested for anxiety behavior on the EPM. Rats pre-treated with amphetamine exhibited significantly increased anxiety-like behavior on the EPM compared to saline pre-treated rats. However, amphetamine pre-treated rats infused with paroxetine in the vHipp spent more time in the open arms of the maze than amphetamine pre-treated rats infused with vehicle. This suggests that increasing 5-HT in the VHipp is effective in reducing anxiety-like behavior. Taken together, these data suggest that 5HT in the VHipp is important for regulating anxiety behavior during amphetamine withdrawal, and increasing 5HT levels during withdrawal may be an effective mechanism for reducing anxiety-induced drug relapse. Funded by: NIH R01 DA019921. WT was supported by a UDiscover fellowship and a Undergraduate Research Grant, both from USD

83. **Coping profiles, emotional resilience and corticosteroid receptors in male rats: A preliminary analysis.** Thompson, B. Randolph-Macon College; Kirk, E. Randolph-Macon College; Hazelgrove, A. Randolph-Macon College, Bardi, M. Randolph-Macon College; Lambert, K. Randolph-Macon College. In an attempt to explore models of emotional resilience, recent research in our laboratory investigated the neurobiological effects of contingency training on spatial learning and prediction errors in male rats

profiled as passive, active and flexible copers. Due to the observation of associations between high cortisol levels and depression, both corticosteroid (CORT) and dehydroepiandosterone (DHEA) were assessed following baseline and training time points. Following contingency training for four weeks, the animals were exposed to spatial training in the dry land maze. Ninety minutes following the probe trial testing, animals were euthanized and their brains were processed for relevant neurobiological markers of resilience. Results indicated that contingency training resulted in higher DHEA/CORT ratios, suggesting that training enhanced emotional resilience. Coping strategy, however, was associated with neuroplasticity in the hippocampus, with flexible copers exhibiting more doublecortin-immunoreactivity (ir) in the dentate gyrus than the more consistently responding active and passive copers. For the current study, as an additional index of corticosteroid measures associated with both training and coping strategy, brain tissue from the initial study was further processed for glucocorticoid- and mineralocorticoid receptor- (GR and MR, respectively) ir in the dorsal hippocampus. Focusing on GR-ir in the CA1 hippocampus, no effects of training or coping strategy were observed. Although contingent-trained brains were not available, when non-contingent active, passive and flexible copers were examined, a non-significant trend was observed ($p=.09$) indicating the active copers had more MR-ir tissue than the passive and flexible copers. Thus, in addition to altered neuroplasticity in the hippocampus of animals profiled with varying coping strategies, corticosteroid-ir is also differentially activated in these coping groups. This preliminary analysis suggests that further research is necessary at various stress time points to further understand the role of these receptors in animals with various predisposed strategies and contingency-training histories. Considering the involvement of the HPA axis in psychiatric illnesses such as depression, these results provide further evidence of the appropriateness of contingency training and coping strategy profiles as animal models for building resilience against the emergence of depressive-like symptoms.

84. **Involvement of dopaminergic mechanisms in antidepressant activity of leptin in mice.** Cordeiro, R.(1); Tomaz, V.(2); Medeiros, C.(1); Macêdo, D.(2); Carvalho, A.(1); (1) Department of Medical Sciences, (2) Department of Physiology and Pharmacology, Universidade Federal do Ceará. Depression is a prevalent and disabling disorder associated with an increased risk of suicide. Although many patients benefit from current antidepressant drugs, there is still a significant amount of non-responders. The development of novel therapeutics is a key to help unveil the pathophysiologic mechanisms underlying depression. Leptin, a hormone responsible for satiety, is expressed in limbic structures related to mood regulation. Because immuno-inflammatory mechanisms are involved in the pathophysiology of depression, the depressive-like behavior induced by the lipopolysaccharide (LPS) of Escherichia coli has been the subject of extensive research. Therefore, we investigated the antidepressant effect of leptin and the involvement of dopamine (DA) and its cognate receptors in depressive-like behavior induced by LPS. To this end adult male Swiss mice (20 - 30 g, n = 6 - 8 per group) were treated with leptin (1.5 mg / kg, ip), SCH23390 (15 μg / kg, ip, D1 receptor antagonist), raclopride (0.4 mg / kg, ip, D2/D3 receptor antagonist), imipramine (10 mg / kg , ip), LPS (0.5 mg / kg, ip) or saline and divided into seven groups: Saline; Leptin; LPS; Leptin + LPS; SCH23390 + Leptin + LPS; Raclopride + Lep + LPS; Imipramine + LPS. Drugs within groups were administered 30 minutes apart. 24 h following LPS treatment mice were submitted to behavioral assessments of open field, forced swimming (FST) and sucrose preference (SPT) tests. The statistical analysis was performed by ANOVA followed by Tukey's test ($p < 0.05$). Treatment with LPS increased immobility time in FST and decreased sucrose preference in SPT. The locomotor activity without significant difference excluded that the increased immobility time of LPS was caused by sickness behavior. Leptin was able to prevent behavioral changes induced by LPS in FST and SPT, thereby showing and confirming the antidepressant action of leptin. Treatment with DA receptor antagonists inhibited leptin's activity in FST, but did not show any changes in SPT. Therefore, this indicates that DA and its receptors play an important role in the pathophysiology of the disorder further studies are taking place regarding DA in depression.

85. **Reduced social behavior and heightened anxiety in 5HTT knockout Mice.** McBratney, M., Gibson, C., Miranda, B., Lugo, J. and Martin, L. A. Dept. of Graduate Psychology, Azusa Pacific University, Azusa, CA. The serotonin transporter (SERT or 5HTT) is a monoamine transporter protein that recycles serotonin back into presynaptic neurons following its release into the synapse. 5HTT knockout mice show depressive-like behaviors, increased anxiety-like behaviors, and a selective deficit in the extinction recall of fear memory. The goal of the current study is to determine the role of 5HTT in social behavior. Homozygous and heterozygous 5HTT knockout mice were compared to wildtype siblings in a series of testing paradigms aimed at exploring social behavior. In the first paradigm, social affiliation was assessed by tracking the movements of test mice in an open arena using the ANY-Maze video tracking system. Mice were free to choose between a social partner housed in a pencil cup in one corner of the arena or an empty pencil cup in the opposite corner. In the second paradigm, social recognition was assessed by video tracking of mice that have a choice between a familiar social partner housed in one pencil cup and a novel partner housed in the opposite pencil cup. 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. In the valence comparison task, motivation for a food reward was compared to a social reward. The mice were conditioned to associate one lever consistently with a food reward and another consistently with a social reward allowing a preference choice. To date, a total of 22 mice have been tested in the social behavior paradigms. Genotyping revealed that there were only 7 +/- and 4 -/- 5HTT mice in this initial cohort. Preliminary ANY-Maze results are inconclusive in regards to social behavior but activity data demonstrated that the 5HTT -/- mice spent more time in the perimeter and less time in the center of the empty arena than the +/+ mice. Data from the social motivation task showed that the -/- mice demonstrated fewer lever presses for a social reward than the +/- and +/+ mice. Early indications suggest that 5HTT -/- mice exhibit greater anxiety and reduced social motivation than +/+ mice. The evidence of heightened anxiety is consistent with previous studies on 5HTT knockout mice. The findings of reduced social motivation extend the list of functional deficits associated with this gene.

86. **Effects of Social Environment on Motor and Spatial Behavior in Rats Exposed to Moderate Levels of Ethanol or Saccharine During Gestation.** Magcalas, C.M. University of New Mexico Department of Psychology; Rodriguez, C.I. University of New Mexico Department of Psychology; Barto, D. University of New Mexico Department of Psychology; Rice, J.P. University of New Mexico Department of Psychology; Fink, B.C. University of New Mexico Department of Psychology; Bird, C.W. University of New Mexico Department of Psychology; Davies, S. University of New Mexico Department of Neurosciences; Savage, D.D. University of New Mexico Department of Neurosciences; and Hamilton, D.A. University of New Mexico Department of Psychology. Fetal alcohol exposure is associated with structural and physiological changes that impact the central nervous system and can result in persistent negative consequences in a broad spectrum of cognitive and behavioral domains including deficits in motor behavior, social behavior, and behavioral flexibility. Previous studies have identified housing manipulations including social environment as potentially important factors that could modulate a wide range of behavioral consequences of ethanol (EtOH) exposure. In the current study tongue protrusion and flexible spatial behavior in the Morris water task (MWT) were measured in adult rats exposed to saccharin (SAC) or EtOH during gestational development under two housing conditions; rats were housed with a single cage-mate from either the same or different prenatal diet condition. Rat dams voluntarily consumed either 0% or 5% EtOH for a 4 hour period daily over the entire gestation period. After weaning rats were pair-housed in either EtOH-EtOH, SAC-SAC or EtOH-SAC pairs. The 24 male offspring were tested in adulthood (PD90-120) on tongue protrusion and in a variant of the MWT in which rats were initially given 40 training trials to navigate to one location, such that direct swims were well-established, followed by 24 trials in which the platform was relocated to the opposite side of the

pool. For tongue protrusion there were significant effects of prenatal diet (EtOH < SAC) and cage-mate diet condition (different < same). The interaction was not significant, as cage-mate diet condition was associated with equivalent reductions in EtOH- and SAC-exposed rats. In the MWT there was a significant prenatal diet X cage-mate diet interaction for the number of visits to the initial location during the platform relocation trials. The interaction was due to a significant prenatal diet effect for rats housed with same diet condition partners (EtOH > SAC) that was not observed for different diet condition housing (EtOH = SAC). More specifically, the number of visits to the initial platform location was low in SAC rats housed with SAC-exposed partners, but comparable and significantly higher in all other combinations of prenatal diet and housing factors. These outcomes suggest that social environment related to cage-mate diet can have negative consequences for EtOH and SAC-exposed rats in behaviors that require and engage circuitry known to be influenced by social housing manipulations. [Supported by grant AA019462 to DH].

87. **The role of PACAP in motivationa effects of nicotine.** Prableen Singh, Andy Tseng, Abdul Hamid, Paul Marquez, Anita Khisravan Ahoura and Kabirullah Lutfy. Nicotine addiction is a major 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 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. 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 PACAP heterozygous mice consumed more nicotine compared to wild-type mice at the two higher concentration of nicotine. Together, the current results suggest that PACAP and its receptors may be a novel target for the development of nicotine addiction and smoking cessation.

88. **The effects of wheel running exercise on opioid withdrawal-induced conditioned place aversion in mice.** K. Wihbey and C.J. Heyser. Department of Neurosciences, University of California, San Diego, School of Medicine, La Jolla, CA 92093. Considerable research has been focused on the neural mechanisms underlying opiate dependence following chronic administration, primarily examining factors associated with the maintenance of an established state of dependence. However, it is clear that opiate antagonsits can elicit signs resembling opiate withdrawal following a single exposure to morphine, a phenomenon referred to as acute dependence. Additional morphine exposure at daily or weekly intervals results in further increases in withdrawal severity, suggesting that acute opioid dependence reflects the early stages of the development of a chronic dependence. The present study was conducted

to examine the effects of a behavioral manipulation (exercise/activity) on the aversive properties of acute morphine withdrawal in mice using a conditioned place aversion (CPA) model. Conditioned place aversion is known to be a sensitive measure of the aversive motivational state produced by opioid withdrawal in rodents. Wheel running is a common model for exercise in rodents and has been shown to have reinforcing properties, an effect that has been linked to the endogenous opioid system. In the present study, separate groups of adult male C57BL/6J mice were given two-hour access to running wheels for eight days either before place conditioning or after place conditioning. To induce CPA, naloxone (0.32 mg/kg) was administered 4 h after a subcutaneous injection of morphine (10.0 mg/kg), immediately prior to confinement to one compartment of the conditioning apparatus; mice received two such naloxone-conditioning trials (separate by 48 h). As expected, acute opioid withdrawal produced a reliable CPA. The magnitude of CPA was significantly decreased in animals that had access to wheel running either before or after conditioning. Therefore, it appears that exercise may decrease the aversive properties of acute opioid withdrawal. Taken together with previous research, we suggest that the attenuation in CPA may be due to neuroadaptions in the endogenous opioid system resulting from wheel running and morphine exposure. Future studies using chronically dependent animals are needed to determine if exercise might be included as a useful treatment for opioid-dependent patients who are in an abstinence period. Information derived from this model may contribute to our understanding of the switch from initial experimentation and casual use of a drug to compulsive use or addiction.

89. **The role of opioids in the reinforcing actions of sugar.** Anita Khosravan Ahoura, Andy Tseng, Abdul Hamid, Prableen Singh, Paul Marquez and Kabirullah Lutfy. Sugar addiction is a major public health and socioeconomic issue. However, limited information is available on the underlying mechanism of reinforcing action of sugar, which may be responsible for its addictive properties. The endogenous opioid system has been implicated in motivational effects of sugar and other palatable food. However, the role of each opioid peptide in this response is less clear. Thus, the present study was designed to assess the role of beta-endorphin and enkephalins in reinforcing actions of sugar. Mice lacking beta-endorphin or enkephalins and their respective wild-type littermates/controls were trained in the operant conditioning paradigm to obtain a 12% sugar solution on a fixed ratio 1 (FR1) of reinforcement. Mice lacking beta-endorphin and their wild-type littermates learned quickly to press the active lever to obtain the sugar solution and this response decayed upon extinction training when water was replaced for sugar solution. However, when sugar became available, these mice quickly maintained their level of lever pressing and intake. Nevertheless, we observed no difference between wild-type and knockout mice in either phase of the conditioned response. On the other hand, mice lacking enkephalins appeared to learn the response at a slower pace compared to their wild-type littermates although they exhibited extinction and reinstatement similar to the wild-type mice. Together, these results suggest that enkephalins may be involved in sugar reinforcement/consumption. We also conducted western blot analyses, where we divided wild-type mice into high (HR) and low responders (LR) based on their performance in the operant conditioning experiments and measured the level of phosphorylated extracellular protein kinase (pERK) in different brain regions. Our results showed high levels of pERK expression in the striatum of HR mice. Given that ERK is upstream of c-Fos, these results suggest heightened level of neuronal activity in this brain region of HR mice. Studies are underway to determine changes in other brain regions in the level of pERK and whether there are differences in the level of ERK activation between mice lacking enkephalins and their wild-type littermates/control. Studies are also underway to assess the role of endogenous dynorphins in these processes.

90. **Social learning enhancements may be due to rapid estrogenic action in the hippocampus.** Ervin, K.; Moore, A.; Sinclair, K.; Choleris, E.: Dept. of Psychology, University of Guelph, Guelph, ON N1G 2W1 Canada. Social learning is the process by which humans and animals can gain adaptive information from their environment from another group member, thereby avoiding costly trial and error

learning. The social transmission of food preferences (STFP) is a form of social learning in mice. In this task, an observer interacts with a demonstrator which has recently eaten a novel flavoured food. When later tested for a food preference, the observer prefers the food it encountered on the demonstrator's breath. Estrogens modulate performance on this task, and we have found that 17β-estradiol (E2) improves social learning in the STFP on a rapid time scale, within 45 min of treatment. This is in contrast to the better known long-term effects of estrogens, which affect behavior on a scale of hours to days. The brain regions involved in the rapid estrogenic enhancement of social learning in the STFP are yet unknown, but the hippocampus appears a likely candidate. Systemic E2 rapidly increases dendritic spines in the CA1 hippocampus (Phan et al 2012, Neuropsychopharm: 2299), intrahippocampal E2 rapidly enhances learning in nonsocial learning tasks (Phan et al 2012, SfN abstracts: 92.12), and hippocampal lesions cause impairment in the STFP (Alvarez et al 2001, Learn Mem: 79; Bunsey & Eichenbaum 1995, Hippocampus: 546). To assess the role of the hippocampus in the rapid estrogenic modulation of learning in the STFP, we implanted female ovariectomized CD1 mice with bilateral guide cannulae aimed at the CA1 hippocampus. Observer mice were infused with 0.5μL (per side) of vehicle, 25, 50, or 100nM E2 into the CA1 hippocampus 15 min prior to a brief social interaction with a female ovariectomized demonstrator. Measurements of food preference were taken at 30 min and 2, 4, 6 and 8h intervals during the choice test. The first measurement was therefore 45 min after treatment, ruling out long-term genomic effects of E2. We also tested observers with a difficult version of the STFP in which control animals showed no learning, allowing us to see enhancing effects. Preliminary results suggest that infusions of 25nM E2 may rapidly improve learning on the STFP, indicating that the hippocampus may be one site at which estrogens act to enhance social learning. These results provide evidence for the role of the hippocampus in the STFP and elucidate the neural mechanisms underlying estrogenic rapid improvements of learning. Funded by NSERC.

91. **MDMA enhances the extinction of cued fear memory in mice.** Young, M. Yerkes National Primate Research Center, Emory University; Howell, L. Yerkes National Primate Research Center, Emory University. In the past five years, clinical studies have reported long-term alleviation of post-traumatic stress disorder (PTSD) symptoms by combining psychotherapy with acute 3,4-methylenedioxy-N-methylamphetamine (MDMA, 'ecstasy') treatment. Up to this point, many studies had investigated the detrimental effects of long-term and binge MDMA use on cognition and brain function. However, between the relative dearth of research into its cognitive effects and its wide range of neuropharmacological effects, it is difficult to interpret the mechanisms by which acute MDMA treatment helps to treat PTSD. Pavlovian fear conditioning in mice is a useful model for understanding how the powerful memories for frightening experiences are acquired and stored in the brain, and subsequent extinction of fear memory by repeated re-exposure to the conditioned stimulus is similar to exposure therapy in humans. Here, we report that combining sub-optimal extinction training with pre-training treatment with MDMA (7.8 mg/kg) enhances retention of extinction memory up to at least 2 weeks later. Interestingly, when extinction retention was tested in a context different from the extinction training environment, only MDMA-treated animals exhibited any extinction whatsoever, suggesting that MDMA promotes both safety signal learning and generalization of extinction. MDMA has a variety of effects on neuromodulatory systems, including serotonin, dopamine and oxtyocin systems, all of which are important for socio-affective behavior. We used pharmacological manipulations to begin to determine which effects of MDMA facilitate fear memory extinction. Among the systems explored, we investigated the serotonin 2A receptor, which has been shown to be important for fear memory extinction and also is a target for psychedelic compounds like MDMA, which have been shown in recent studies in humans to be useful in the treatment of affective disorders. These and subsequent studies will be important for understanding how short-term MDMA treatment helps to treat PTSD, and will potentially help to develop strategies for optimizing treatment outcomes.

92. **Deep brain stimulation in an animal model of schizophrenia: treatment and prevention.** Bikovski, L. School of Psychological Sciences and Sagol School of Neuroscience, Tel Aviv University; Weiner, I. School of Psychological Sciences and Sagol School of Neuroscience, Tel Aviv University. Schizophrenia (SCZ) is a devastating brain disorder with profound disruptions in cognition and emotion whose pharmacotherapy remains unsatisfactory. Deep brain stimulation (DBS) of specific brain regions has been approved for the treatment of movement disorders and treatment-resistant psychiatric disorders like OCD. On theoretical grounds as well as animal studies it has been suggested that DBS would be effective also in SCZ but more evidence is needed. The present study tested the possibility that DBS of the prefrontal cortex, a core region implicated in the pathophysiology of SCZ, will alleviate and/or prevent a SCZ-like attentional deficit in a neurodevelopmental animal model of the disorder based on a known environmental risk factor, prenatal infection/immune activation. Maternal immune activation was induced by administering the viral mimic polyinosinic-polycytidilic acid (poly I:C) on gestation day 15, which has been shown to produce a broad range of SCZ-relevant brain and behavioral abnormalities. SCZ-like attentional deficit was assessed in the adult offspring by measuring latent inhibition (LI), a cross-species selective attention phenomenon reflected in poorer conditioning to a previously irrelevant compared to a novel stimulus, which is disrupted in SCZ patients and offspring of poly-I:C exposed dams. DBS (bilateral; frequency 150 Hz; pulse width 100 μs; current intensity 150 μA; charge density 7.612μC/cm2/ph) of the medial prefronatal cortex (mPFC;3.5 mm anterior to bregma, 0.6 lateral to midline and 3.4 ventral to dura) was administered either acutely to adult offspring during LI training, or chronically in adolescence (postnatal days 33-44), when SCZ-like LI deficit is still absent. As found previously, control (sham-stimulated) adult offspring of poly-I:C exposed dams failed to show LI. LI was present in poly-I:C offspring which were stimulated during the LI task, but stimulation disrupted LI in controls. DBS given in adolescence prior to the emergence of LI deficit prevented the emergence of such deficit in poly-I:C offspring. Notably, this stimulation regime did not affect LI in controls. Given that attentional deficit is central to SCZ, these results suggest that DBS of the mPFC may be beneficial as a therapy/prevention in this disorder. Furthermore, given that DBS is believed to interact with dysfunctional neuronal networks, the efficacy of chronic stimulation suggests that early DBS may act by normalizing aberrant brain connectivity.

93. **Enrichment improves responses to anxiogenic stimuli and modifies dendritic morphology of striatal and hypothalamic neurons in trait anxiety rats.** Donaldson, S.T.1; Ravenelle, R.2; Lott, R.1; Gildersleeve, E.1; Bharadwaj, P., Park, J.H. 1Developmental and Brain Sciences, Psychology Department, University of Massachusetts Boston, Boston, MA USA; 2Department of Biological Sciences, Fordham University, Rose Hill Campus, Bronx, NY USA. The enriched environment (EE) offers visual, social, tactile stimulation as well as exercise and serves to improve anxiogenic and stimulant drug responses in trait anxiety animals. Given that EE can lead to enduring neurobehavioral changes, we evaluated whether any microstructural alterations in pyramidal neurons of the nucleus accumbens (NAc) and hypothalamus might parallel any benefits of EE. Sixth generation adult male Long Evans rats from preexisting high (HAn) and low (LAn) anxiety lines showed anxiety-like behavior (ALB) in the elevated plus maze (EPM) and open field activity (OFA), and hyperactivity to amphetamine (AMPH: 0.5 mg/kg, IP). Following EE, ALB was reversed with HAn showing increased %OA entries and time and greater OFA center activity and the AMPH response was attenuated. We assessed dendritic length alterations by analyzing representative brains stained using a rapid Golgi-Cox method. We found that two dendritic qualities were changed for HAn EE animals, the mean apical dendritic length and spine density were increased. Taken together, these data suggest that (i) ALB can be reliably demonstrated in our HAn anxiety line, (ii) postnatal EE can serve to protect against ALB and elevated AMPH responses in HAn animals, and (iii) this protection may be related to structural changes in dendrites of pyramidal neurons located in the NAc and hypothalamus.

94. **Neuronal circuits underlying transfer of remote emotional information in mice.** Meyza K., Nencki Institute of Experimental Biology, Nikołajew T., Nencki Institute of Experimental Biology, Kondrakiewicz K., Nencki Institute of Experimental Biology, Sadowska J., Nencki Institute of Experimental Biology, Knapska E., Nencki Institute of Experimental Biology. Empathy is often considered a human-specific trait, but growing evidence suggests that other animals also display behavioral adjustments upon exposure to remote emotional information from conspecifics. Since lack of empathy is one of the core features of autism spectrum disorder (ASD), it is crucial to develop animal models to study neuronal correlates of this impairment. In order to do that we employed a behavioral paradigm used previously for rats (Knapska et al. 2006, 2009). In the current study we used c57BL/6J mice, housed in pairs for 4 weeks prior to the onset of the experiment. The animals were habituated to being handled, transported and to brief separation (10 min) for at least 10 days. On the test day, one of the mice (Demonstrator) was removed from the cage, moved to the conditioning chamber and either left undisturbed or subjected to fear conditioning training. The other mouse (Observer) was left undisturbed in the home cage. After the animals were reunited in their home cage, their behavior was recorded for 10 minutes. The Observers exposed to stressed Demonstrators exhibited an increase in the number and duration of contacts, the number of nose-to-nose and nose-to-anogenital sniffs and an increase in the number and duration of digging episodes as compared with the Observers exposed to non-stressed Demonstrators. This was accompanied by a strong increase in the expression of c-Fos protein in the prelimbic and infralimbic medial prefrontal cortex and the basolateral and central (lateral part) nuclei of the amygdala. No such change was observed in other parts of the amygdala or in the ventral hippocampus. The level of c-Fos protein expression in the basolateral nucleus of the amygdala was similar in both animals from pairs in which Demonstrators underwent fear conditioning training. In central (lateral part), medial and cortical nuclei of amygdala, the CA1 field of the ventral hippocampus and both prelimbic and infralimbic medial prefrontal cortices the expression in the Observers in these pairs was lower than that in the Demonstrators. These neuronal correlates of transfer of remote emotional information will serve as a reference for studying empathic behaviors in mouse models of autism.

95. **Win-related cues drive risky decision-making on a rodent Gambling Task.** Michael M. Barrus (University of British Columbia), Catharine A. Winstanley (University of British Columbia). Animal models of gambling behavior allow insight into the neurobiology of gambling that is otherwise lacking because of technical, practical and ethical limitations of human research. Our laboratory has developed a model of gambling behavior for use with rodents called the rodent Gambling Task (rGT). The rGT allows animals to choose between four options that are associated with varying levels of risk and reward; the optimal strategy on the task is to choose the option with a relatively small reward but also infrequent punishment, allowing the animal to collect the maximum amount of reward over the course of the 30 minute session. Animals quickly learn the task, and their behavior has been well characterized; most animals adopt an optimal strategy and perform well on the task, while some behave in a riskier manner, preferring a high-risk, high-reward strategy, much like a high-stakes human gambler. A new version of the rGT incorporates flashing lights and tones to signal wins. These win cues are not proportional to the win size; as in a human gambling paradigm, the win-related cues are exponentially larger for large wins, making these options more attractive despite the fact that they are ultimately disadvantageous over the course of a session. It appears that the addition of these cues is enough to drive a detrimental, risk-seeking pattern of behavior, as rats trained on this task show a higher preference for the risky options than rats trained on the uncued version of the task. Current work is aimed at delineating the specific contributions of catecholamines to this behavior, with a focus on dopaminergic D2-like receptors. The use of the rGT provides greater insight into the neurobiology of gambling, especially risky decision-making in the face of uncertain or probabilistic outcomes. This research should enable a better understanding of how and why salient cues shape the decision-making process.

96. **Chronic LPS-induced Inflammatory Response in a Diabetic Model of Alzheimer's Disease.** Andrew S. Murtishaw, Chelcie F. Heaney, Monica M. Bolton, and Jefferson W. Kinney; Department of Psychology, Division of Neuroscience, University of Nevada, Las Vegas. Alzheimer's disease (AD) is a neurodegenerative disorder of unknown etiology. AD is characterized by cognitive and behavioral impairments in addition to pathological features that include amyloid plaques, neurofibrillary tangles, and neuronal loss. Only a small proportion of AD cases are due to genetic mutations (familial AD), whereas the vast majority of cases are late onset and sporadic in origin. The cause of sporadic AD (sAD) is likely multifactorial, with interactions of external factors, biological, and genetic susceptibilities that contribute to the onset and and progression of the disease. Diabetes Mellitus (DM) and neuroinflammation are two of the most common risk factors that have been implicated in sAD. Considerable progress has been made to understand the involvement of each of these risk factors in isolation but limited data exist on the combination of the two. In order to evaluate any interactions between DM and inflammation in AD we are investigating the effects of neuroinflammation in a diabetic-model of sAD on behavioral and pathological markers. Previous research in our laboratory has demonstrated that a one-time acute inflammatory response (LPS administration) in the diabetic model of sAD (utilizing streptozotocin; a compound used to dysregulate insulin signaling in the brain) produced subtle improvements in a spatial learning task. Our data further demonstrated that STZ animals that underwent the immune activation did not exhibit as robust an elevation of oligomeric beta-amyloid compared to the STZ alone group. The current investigation is directed at determining the effects of a chronic inflammatory response on STZ-induced deficits relevant to AD. One week following the STZ infusion, LPS was administered twice per week for 8 weeks in order to chronically activate the immune system. Learning and memory was examined in the novel object recognition and Morris water maze tasks, following which hippocampal tissue is being examined for pathological markers of AD.

97. **Acute cocaine administration decreases advantageous decision-making but does not affect impulsive action as measured by a rodent gambling task.** Ferland, J-M. N. (Dept. of Psychology), Tremblay, M.(Dept. of Psychology), Adams, W.K.(Dept. of Psychiatry), Winstanley, C.A(Dept. of Psychology). Drug addiction is a prolific behavioural disorder that poses a worldwide health concern. Higher levels of impulsivity and maladaptive decision-making are common behavioural traits found amongst substance abusers and are thought to play an integral role in drug use. Human studies using the Iowa Gambling Task (IGT) a validated measure of decision-making, have found that substance dependent individuals tend to make poorer choices and are less likely to change their strategy following losses compared to controls. However, the majority of these studies and similar animal work have been done with chronic cocaine administration. To our knowledge, no work has been completed investigating the relationship between acute cocaine administration and decision-making behaviour. To investigate this relationship, we trained 16 rats on the Rodent Gambling Task (rGT), a rodent analogue of the IGT designed to assay decision-making and impulsive action. 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 goal of the task is to maximize the amount of reward received within a 30 minute session. Following training on the task, the animals were administered 5, 10, or 20 mg/kg of cocaine via i.p. injection or saline vehicle prior to engaging in the task. We found that, compared to saline, the medium dose of cocaine resulted in a decrease in the most advantageous choice option while choice of the slightly less advantageous option increased significantly, indicating a shift away from adaptive decision-making. Similarly administration of the high dose of cocaine significantly decreased choice of the advantageous option, but was also accompanied by significant increases in omissions, a common effect of high doses of psychostimulants. Interestingly, impulsive action as measured by premature responses on the task was not affected by acute cocaine exposure. These data indicate that singular cocaine

administration may be enough to initiate changes in decision-making behaviour, providing a foundation to understand how these behaviours involved in addiction begin and change following chronic cocaine exposure.

98. **Prefrontal GABA modulation of working memory processes.** Meagan L. Auger & Stan B. Floresco, Department of Psychology, University of British Columbia. Reduced expression of markers for GABA within the prefrontal cortex (PFC) is consistently observed in schizophrenia, and may lead to cognitive deficits associated with the disorder. Recent studies have shown that blockade of prefrontal GABAA receptors increased response latencies but did not impact accuracy in the delayed-response working memory task conducted on a radial maze. However, the possibility remains that tasks which place higher demands on attention and requiring resistance to 'proactive interference' may be more sensitive to PFC GABA dysfunction. Thus, the goal of this study was to explore whether PFC GABA transmission impacts these different aspects of working memory. Separate groups of rats were trained on one of two tasks. In the massed-trials reference/working memory task, rats were trained to retrieve a food from the same 4 arms of an 8-arm radial maze, where they received massed training designed to increase proactive interference (5 trials per day, 1-2 min ITI). The delayed non-match to position (DNMTP) task consisted of a sample phase, in one of two levers was extended, and a choice phase, requiring selection of the opposite lever, separated by a variable delay (1-24 s). Well-trained rats received intra-mPFC infusions of saline and either the GABAA antagonist, bicuculline (12.5 or 50 ng), or the GABA agonists baclofen and muscimol (100 ng each). Blockade of PFC GABAA receptors caused a pronounced increase in working and reference memory errors in both the first and subsequent trials of the radial arm maze task, as has been observed in schizophrenic patients. In contrast, PFC inactivation did not affect performance of this task. PFC GABA blockade also induced delay-independent impairments in accuracy on the DNMTP task. Taken together, these results indicate that PFC GABA blockade induces working and also spatial reference memory deficits that are distinct from the effects of PFC inactivation, and resemble deficits observed in schizophrenia.

99. **Maternal peri-conceptional cortisol and HPA axis activity in pre-pubertal children.** Barha, C. Maternal and Child Health Laboratory, Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada; Salvante, K. Maternal and Child Health Laboratory, Faculty of Health Sciences and Human Evolutionary Studies Program, Simon Fraser University, Burnaby, Canada; Blais, J. Department of Statistics and Actuarial Sciences, University of Waterloo, Waterloo, Canada; Ma, H. Department of Statistics and Actuarial Sciences, University of Waterloo, Waterloo, Canada; Zeng, L. Department of Statistics and Actuarial Sciences, University of Waterloo, Waterloo, Canada; Nepomnaschy, P. Maternal and Child Health Laboratory, Faculty of Health Sciences and Human Evolutionary Studies Program, Simon Fraser University, Burnaby, Canada. Adverse prenatal conditions appear to have negative consequences for development and disease susceptibility across the lifespan. Exposure to maternal stress during pregnancy may influence children's behavioural, emotional, cognitive, immune and metabolic functioning. Most of this evidence is derived from research focused on the gestational period following the clinical detection of pregnancy (> week 6). However, crucial epigenetic processes are known to take place earlier, during the first six gestational weeks (peri-conceptional period), which we hypothesize represents a critical window of vulnerability. To test this hypothesis, we evaluated the relationship between maternal peri-conceptional cortisol and children's pre-pubertal HPA axis activity in 18 mother-child dyads. We quantified cortisol levels in first morning urinary specimens collected every other day from mothers during the first six gestational weeks. Then, 12 years later we evaluated HPA axis activity in the children for three weeks as they began a new school term, a known non-experimental stressor. Using linear mixed models we found that maternal cortisol during week 5 of gestation was positively associated with children's cortisol levels prior to ($p = 0.03$) and after the non-experimental stressor (first day of school; $p = 0.028$). Children's cortisol trajectories during the two weeks after the start of school

varied with their mother's cortisol during week 1 of gestation (p = 0.02). Furthermore, maternal cortisol during week 2 of gestation predicted whether their child habituated to the non-experimental stressor (cortisol returned back to levels seen prior to the first day of school) within two weeks. The odds of a child habituating increased 5.53% for every percentage increase in their mother's week 2 cortisol (p = 0.054). Children's salivary cortisol levels in response to an experimental stressor (Tier Social Stress Test-Child) was marginally associated with maternal cortisol during week 2, and this effect was stronger in males than in females (interaction p = 0.067). Our results suggest that peri-conceptional stress levels may affect HPA axis ontogeny and postnatal stress responsivity. Further research is needed with larger samples sizes to confirm these results and to explore the offspring epigenome as a potential mechanism through which maternal peri-conceptional cortisol may program the HPA axis.

100. **Treating psychotic patients with agonist opioid therapy and atypical antipsychotics.** Pieri M.C.;Comaschi A.C. The aim of the study is To evaluate the efficacy of olanzapine in patients maintaining methadone; 2. To explore time-course variation of craving and weight at baseline and every 2 months for the first 6 months and then every 6 months until the end of the study (30th months). 3. To compare symptoms severity between patients on methadone and patients on buprenorphine Patients were enrolled from the East Out-patient Addiction Unit (SER.T) of Bologna, Italy. All signed a written informed consent. 32 received methadone and 13 buprenorphine. 36 were included into three treatment subgroups At baseline and follow-up sessions the following rating scales were administered: The Minnesota Multiphasic Personality Inventory-2 (MMPI-2 The Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) Bech-Rafaelsen Mania and Melancholia Scales (BRMAS, BRMES; Bech et al. 1988) covering severity of manic and depressive symptoms respectively. The VAS (Visual Analogic Scale) to quantify craving for drugs Statical result A significant difference was found among the 3 subgroups in Baseline, Supplementary and Content Scale The frequency of personality disorders at baseline was 72.2% At the end of study, significantly reduced BRMES and BRMAS scores were found in all subgroups, particularly in the "olanzapine+methadone" subgroup. Total and partial at BRMES and BRMAS scores did not significantly change during the follow-up period (6th-30th month), even if the curve displays a downward trend VAS total scores were significantly lower both at 6th and 30th month None of the three treatments induced a significant weight gain both after 6 months (at this time session we observed better results The association of methadone to olanzapine even in presence of subthreshold psychiatric symptoms improve treatment adherence in substance abusers

101. **Investigation of anxiety, neuronal injury, and vGluT2 and CRH expression following pre-ischemic administration of cannabinoid receptor 1 antagonist, AM251, in male rats.** Azogu, Idu; Dunbar, Megan; Barra de la Tremblaye, Patricia; Plamondon, Helene. University of Ottawa. Endocannabinoids can play a modulatory role in emotional brain circuitry and neuroendocrine stress activation. In the current study, we assessed the neuroprotective actions of type 1 cannabinoid receptor (CB1) antagonist, AM251, on neuronal injury, dopaminergic transmission changes, excitotoxicity and stress response, and behavioral deficits post ischemia. 4 groups of male Wistar rats (n=10 per group) were pretreated with AM251 (2mg/kg, i.p.) or saline 30 minutes prior to sham or global cerebral ischemia. After 5 days of recovery, animals were exposed to the open field and the elevated plus maze tests. Rats were killed 7 days post ischemia and immunohistochemical detection was performed. Our findings support a partial or full reversal by AM251 of ischemia-induced reduction in dopamine transmission (tyrosine hydroxylase and dopamine D1 receptor expression) in mesolimbic brain regions including the ventral tegmental area and basolateral amygdala (BLA). Interestingly, AM251 significantly reduced vesicular glutamate transporter 2 expressions in the BLA and paraventricular nucleus, independent of the ischemic/sham condition. Compared to all sham groups, elevated corticotropin-releasing hormone (CRH) expression in the ischemic condition was reduced by AM251. Finally, AM251 reduced CA1 neuronal injury, and

prevented ischemia-induced changes in anxiety. AM251 pretreatment prior to global cerebral ischemia has beneficial effects on neuronal survival and behavior, alleviates reduced dopaminergic transmission, and regulates CRH expression in brain areas related to anxiety and stress.

102. **Unraveling the role of GABA-B receptors on attentional performance, impulsivity and compulsivity.** Vlachou, S. School of Nursing and Human Sciences, Faculty of Science and Health, Dublin City University, Glasnevin, Dublin 9, Ireland; Campos, A. Department of Psychiatry, School of Medicine, University of California, San Diego, La Jolla, CA 92093-0603, USA; Kaczanowska, K. Department of Pharmacology, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, CA 92093-0657, USA; Finn, M.G. School of Chemistry & Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332-0400, USA; Markou, A. Department of Psychiatry, School of Medicine, University of California, San Diego, La Jolla, CA 92093-0603, USA. γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and is implicated in the modulation of central reward and cognitive processes. Numerous studies have shown that γ-aminobutyric acid B (GABAB) receptor antagonists show cognitive enhancing effects. However, little is known about the effects of GABAB receptor agonists or positive allosteric modulators (PAMs) in cognitive processes (e.g., attentional performance) and impulsivity/compulsivity. GABAB receptor PAMs may be potentially improved therapeutic compounds for the treatment of disorders, such as drug dependence, or cognitive impairment, than GABAB receptor agonists due to fewer adverse side-effects. This study aimed to assess the effects of the GABAB receptor agonist CGP44532 and the GABAB receptor positive modulator BHF-177 in attentional performance and impulsivity/compulsivity, as well as the potential cognitive enhancing effects of the GABAB receptor antagonist CGP55845 by using the 5-choice serial-reaction time task (5-CSRTT) in rats. The GABAB receptor agonist CGP44532 significantly affected responding in all measures assessed in the 5-CSRTT at the highest dose tested, indicating a non-specific response-suppressive effect, while the GABAB receptor positive modulator BHF-177 only minimally affected some of the measures assessed in the 5-CSRTT at the highest dose tested, indicating minor specific attentional disruption. Further, the GABAB receptor antagonist CGP55845 did not significantly affect any of the measures assessed in the 5-CSRTT under baseline conditions. Interestingly, rats exhibited a decrease in attentional performance and an increase in inhibitory functions when the difficulty of the task was increased (i.e., by decreasing the stimulus light duration), an effect that was not blocked by the GABAB receptor antagonist CGP55845. In accordance with previous studies, these data suggest that the GABAB receptor positive modulator BHF-177 showed significantly fewer adverse effects than the GABAB receptor agonist CGP44532 in the 5-CSRTT. Support: Grant U19 DA26838 to AM; Post-doctoral TRDRP fellowship (18FT-0048; State of California, USA) to SV; Travel award by the School of Nursing and Human Sciences and the Faculty of Science and Health, Dublin City University, Ireland, to SV.

103. **Effects of permethrin on the acoustic startle response in adult male Sprague-Dawley rats.** Vorhees, C.V.(1), Osimitz, T.(2), Sheets, L.(3), Minnema, D.(4), Brooks, M.(5), Gammon, D.(6), and Williams, M.T.(1). (1)Cincinnati Children's Research Foundation, (2)Science Strategies, LLC, (3)Bayer CropScience, (4)Syngenta Crop Protection, (5)Ag-Chem Consulting, (6)FMC Corporation. Pyrethroids are synthetic insecticides derived from natural pyrethrins. At high doses, Type I pyrethroids induce tremor and Type II induce rolling, limb movements, and salivation. Both types act on voltage-gated sodium channels and some also affect calcium and chloride channels. At sub-symptomatic doses, acoustic startle (ASR) is affected. Type I's induce increases and Type 2's induce ASR decreases. Adult male Sprague-Dawley rats were tested in 2 experiments: Exp-1 assessed ASR 2 h and Exp-2 assessed ASR 2, 4, 6, and 8 h after permethrin (Type I) given by gavage in 5 ml/kg corn oil at doses of 0, 60, 90, or 120 mg/kg (12 rats/group). In addition, in preliminary developmental experiments were conducted at 3 ages (P15, 17 and 21) at doses of 120, 150, and 180 mg/kg. ASR was assessed in 100 trial test

sessions with intertrial intervals of 20 s. Peak response amplitude was recorded on each trial for 100 ms following a 20 ms 120 dB mixed-frequency stimulus. The ASR test apparatus was from San Diego Instruments. Rats were weighed, handled, and pre-tested for ASR prior to treatment. Pretest-1 was an ASR session with no treatment. Pretest-2 (24 h later) was an ASR session after 5 ml/kg corn oil by gavage. Rats were assigned to groups matched for Pretest-2 ASR based on preliminary data that the first day of testing is more variable than on subsequent days. Data were analyzed by ANOVA (Dose x Time x Block; 10 trials/block). No effects were found in Exp-1, 2 h after treatment. In Exp-2, permethrin significantly increased ASR (Dose effect: $p<0.001$; Dose x Time: $p<0.001$; Dose x Time x Block: $p<0.05$). The Dose x Time interaction showed no effects at 2 h; at 4 and 6 h, the mid and high dose groups showed increased ASR; at 8 h, all 3 groups showed increased ASR. In developing rats no effects were seen at 120 mg/kg. Increased ASR was found at 150 and 180 mg/kg but were accompanied by visible tremor. At 180 mg/kg increased mortality also occurred. (Supported by CAPHRA).

104. **Effects of Running Wheel Pre-Exposure on Subsequent Performance on Three Motor Tasks.** Kate F. J. Happel, Kayla Klein-Randall & Susan J. Larson Department of Psychology, Concordia College, Moorhead MN. Previous research has shown that completion of a dowel beam motor task causes activation of molecular markers associated with motor learning. Given the known impact of exercise on learning and brain plasticity, we sought to evaluate whether performance on a dowel beam motor task could be improved with pre-exposure to exercise. In our initial experiment, we exposed six rats to 60 minutes of running wheel access daily for 14 days; control rats received no experimental manipulation during this time. Subsequently, all rats were exposed to three motor tasks. The horizontal ladder task was used to assess forelimb function, while the tapered beam task was used as a measure of hindlimb function. Finally, rats were trained to traverse the dowel beam task, a complex motor task used to assess motor learning. Errors and time to cross the beam were recorded on each of the three tasks. Results indicated that pre-exposure to the running wheel did not improve errors on the horizontal ladder or the tapered beam tasks. However, running wheel pre-exposure did reduce the number of errors made on the dowel task. Running wheel pre-exposure initially improved time to cross the tapered and horizontal beam, however it did not affect time to cross the dowel beam. In a follow up study, we evaluated the effects of running wheel exposure on errors and time to complete the dowel, the horizontal ladder and tapered beam tasks. In this study, four control rats were exposed to an immobile running wheel for the same duration four experimental rats could run in a wheel and order of motor tests was counterbalanced. We found similar results to our initial experiment in that exercise did not decrease time to complete the dowel task, but it did reduce errors on the task. Based on these results, we speculate that running wheel pre-exposure may have improved dowel performance by enhancing brain plasticity. Future studies should evaluate the effects of running wheel exposure through the direct measurement of brain plasticity.

105. **Explorations of creative problem-solving and social responses in free-ranging raccoons: A potential role of von Economo neurons?** Landis, T. Randolph-Macon College; Bardi, M. Randolph-Macon College; Hyer, M. Randolph-Macon College; Rzucidlo, A. Randolph-Macon College; Lambert, K. Randolph-Macon College. Extending our rodent work exploring the influence of effort-driven rewards and effective interactions with the environment on cognitive and emotional resilience, we observed a population of approximately 65 wild, but provisioned, raccoons in Miami FL. Raccoons were presented with a challenging problem-solving task to observe their attention toward relevant aspects of the task as well as their ability to solve the problem (i.e., open a latch). Additionally, they were presented with various novel objects to observe novelty exploration, a response associated with advanced cognitive responses such as creativity. Naturalistic observations revealed that the raccoons displayed both problem-solving and novelty exploration responses. Although not documented in prior studies, extended bouts of social play were observed in adult animals. In a second phase of this exploration, a raccoon brain was processed for Nissl staining so that the presence of von Economo

neurons (VENs), large bipolar neurons, could be determined. Representative VENs were observed in the fronto-insular cortical area, providing, to our knowledge, the first evidence of these neurons in raccoons. VENs, implicated in advanced social responses and self-awareness, may facilitate the socially coordinated responses (e.g., play and social grooming) and persistence in problem-solving tasks observed in these animals. In the future, we plan to investigate additional raccoon brains to assess the distribution patterns of VENs in the ACC and fronto-insular cortex to determine potential similarities with VEN distribution patterns in mammals with larger brains such as apes, elephants and whales.

106. **Chronic hypobaric hypoxia exposure causes memory impairment and modulates hippocampal synaptic strength: Enriched environment as a therapeutic approach.** Vishal Jain, Dipti Prasad, G Ilavazhagan and Shashi Bala Singh, Defence Institute of Physiology and Allied Sciences. Hypobaric hypoxia (HH) is known to cause cognitive dysfunctions owing to the high oxygen dependency of the brain. Cognitive and motor deficits have been reported to occur on chronic exposure to HH. On the other hand various studies have shown that enriched environment enhances learning and memory, reduces memory decline in aged animals, decreases anxiety and increases exploratory activity and also increases dendritic branching and length, the number of dendritic spines and the size of synapses on some neuronal. Present study is designed to explore the effect of enriched environment on hypobaric hypoxia induced memory impairment and alteration in synaptic strength. Sprague dawley rats (3 months old) were exposed to hypobaric hypoxia condition in an animal decompression chamber at an altitude of 25000 feet for continuous 7 days. Animals from control group were kept in standard cage whereas enriched group were kept in enriched environment cage. Following exposure rats were tested in Morris water maze for memory impairment and then sacrificed and hippocampi was dissected out and processed for different experimental protocols. MALDI following 2D electrophoresis was performed to study the global change in hippocampal protein expression. Further expression of different synaptic proteins was assessed through western blotting and immunohistochemistry. Golgi stain was performed to study dendritic arbrorization. Results of the present study showed that identified proteins belong to a diverse variety of functional classes including cell death, proteins involved in oxidative stress metabolism, synaptic proteins, growth factors and proteins associated with signalling. Hypobaric hypoxia decreases expression of synaptic proteins i.e. synaptophysin, PSD-95and synapsin which further validated by western blotting whereas exposing them in enriched environment ameliorate this synaptic loss. Golgi staining reveals protective effect of enriched environment during HH exposure as evident from increased dendritic arborisation, spine density and morphology. Present study also reveals the possible role of BDNF/TrkB signalling in enriched environment mediated modulation hippocampal synaptic palsitcity. Therefore it can be concluded that enriched environment ameliorate HH induced memory impairment and synaptic loss through BDNF/TrkB signalling.

107. **Sex differences in a rat model of risky decision making.** Shimp, K.G., Orsini, C.A., Gilbert, R.J., Willis, M., Bizon, J.L., Setlow, B. (all are at the University of Florida). Sex differences in decision making involving risks have been reported in both humans and animals; however, the "risks" used in laboratory tasks in which risky decision making is assessed typically involve reward omission, rather than actual adverse consequences such as might occur in the real world. To model this type of risky decision making in animals, our lab has developed a "Risky Decision Making Task" (RDT) in which rats choose between a small, "safe" food reward (1 pellet) or a large (3 pellets) food reward accompanied by a variable probability of mild footshock punishment (the "risky" choice). Previous work showed that male Long-Evans rats display considerable individual variability in this task, and that these individual differences are stable across months of re-testing (Simon et al. 2009; 2011; Mitchell et al. 2014). Furthermore, both dopamine D2 receptor agonists and d-amphetamine reliably decrease preference for the large, risky reward in male rats tested on the RDT. Based upon human studies indicating that females display greater risk aversion and sensitivity to punishment than males, the goal of

these experiments was to determine if female Long-Evans rats show greater risk aversion in the RDT (less preference for the large, risky reward) than males, if female risk preference is influenced by estrous cycle, and if d-amphetamine alters risk-taking differently between sexes. Female rats as a group made more risk-averse choices in the RDT than males (fewer choices of the large, risky reward) but showed a degree of individual variability in choice preference that was comparable to male rats. The group difference between males and females in preference for the large, risky reward was not likely due to differences in sensitivity to the footshock, as locomotor activity during shock delivery did not differ between sexes. Risk taking in females was also not modulated by estrous stage, as there were no differences in preference for the large, risky reward across stages of the estrous cycle. Finally, acute systemic administration of d-amphetamine decreased choice of the large, risky reward to a similar degree in males and females. These results suggest that endocrine and/or neurobiological factors not directly related to estrous cycle underlie sex differences in decision making under risk of adverse consequences. Ongoing studies are investigating these possibilities.

108. **The role of dopamine in the active threat responding.** De Oliveira, CC1, de Castro, MC1, Gouveia, FV1, Seno, MDJ1, dos Santos LTC1, Antunes, G1, Fonoff, ET2, Teixeira, MJ2, Otoch, JP2, Martinez, RCR1 1Laboratory of Neuromodulation, Institute of Teaching and Research, Hospital Sirio-Libanese, Rua Coronel Nicolau dos Santos, 69, CEP: 01308-060 - Sao Paulo - SP - Brazil 2University of Sao Paulo, LIM 26 - HCFMUSP, Av. Dr. Arnaldo, 455, 4o. andar - Cerqueira Cesar - CEP: 01246-903 - Sao Paulo - SP - Brazil. Performance of instrumental active avoidance is constrained by Pavlovian defensive reactions such as freezing. Interestingly, in this test we can identify two groups of animals, good performers and poor performers. In this experiment, we attempt to identify the role of dopamine as a modulator of avoidance response in good performers. For that, 47 good performers were trained in the avoidance test for 7 days and in the next day they receive intraperitoneal injection of saline, D2 antagonist - sulpiride (20 or 40 mg/Kg) or D1 antagonist - SCH 23390 (0.025 or 0.05 mg/Kg) and it was evaluated avoidance response and locomotion in the open field test. We showed that D1 antagonist affect threat response by reducing the number of avoidance response in comparison with saline and sulpiride ($F(4,47)=15.10$, $p <0.001$) without affecting the motor system exhibited in the open field test ($F(4,47)=1,72$, $p =0,16$). Thus, this approach suggests that D1 receptors may play important role in the competitive selection of defensive actions vs reactions in threatening situations.

109. **Effects of the antidepressant sertraline given during pregnancy on the dam and the offspring.** Susanne Brummelte, Fairouz A. Shoubah Jennifer M. Kott, Sean M. Mooney-Leber. Department of Psychology, Wayne State University, Detroit, MI, USA. Exposure to maternal medication during pregnancy can have significant impact on the development of the immature brain of the fetus. Many women suffering from depression are successfully treated with anti-depressants today. However, if a woman becomes pregnant while taking anti-depressant she is faced with the difficult question of whether to continue the medication or stop taking the anti-depressants. The current study was conducted to investigate the short and long-term consequences of anti-depressant exposure for different periods of time during gestation in an animal model of depression. First, female rats were treated with a vehicle (oil) or chronic corticosterone (CORT), the major stress hormone in rats, for 21 days to induce depressive-like behavior. After 16 days of CORT or oil treatment, animals were further divided to either receive a daily dose of sertraline (20mg/kg), the most commonly prescribed selective serotonin reuptake inhibitor (SSRI), or vehicle (water). After completion of the CORT/oil treatment, female rats were then paired with males until pregnant and continued to receive sertraline or water either until gestational day (GD) 16 (discontinuation) or 21 (until parturition). The dams were tested in the Forced-Swim Test for depressive-like behavior and the offspring will be investigated at varying stages of development from at neonatal age up to adulthood. We hypothesize that the sertraline treatment will decrease depressive-like behavior in dams and affect the offspring differentially depending if they were exposed until GD16 or

throughout gestation. The identification of time-depend consequences of in utero antidepressant exposure for the unborn offspring will help affected women and their health care providers to make informed decisions regarding their depression treatment.

110. **Activation of basal forebrain GABAergic projection neurons alters mPFC-mediated working memory performance in young F344 rats.** Authors: C. Bañuelos[1], B. Setlow[2], J.L. Bizon[1]; [1]Department of Neuroscience, [2]Department of Psychiatry, University of Florida College of Medicine, Gainesville, FL. Working memory is associated with persistent excitation of pyramidal neurons in the prefrontal cortex (PFC). GABAergic interneurons that project onto pyramidal cells refine spatial and temporal specificity in this system. In addition to intrinsic inhibitory inputs, pyramidal cells in the PFC are influenced by inhibitory projections from basal forebrain. Specifically, GABAergic neurons from the magnocellular preoptic (MCPO) area synapse primarily onto cortical GABAergic interneurons, producing a net disinhibition of PFC pyramidal cells. As such, basal forebrain GABAergic projections are well situated to influence PFC-mediated cognition. To investigate this, adult male F344 rats were surgically implanted with guide cannula aimed at the MCPO and trained on an operant-based delayed response test of working memory. In this task, rats were required to remember the location of a sample lever over a delay period (0-24 s) to obtain a food reward. Basal forebrain GABAergic projection neurons are selectively activated by pharmacologically stimulating M3 receptors. Rats received microinjections of the M3 muscarinic receptor agonist cevimeline (5 µg and 10 µg) or vehicle directly into the MCPO prior to testing in a within-subjects design such that each rat received all drug conditions. Cevimeline microinjections significantly improved working memory at long delays compared to vehicle conditions. These data demonstrate a role for GABAergic HDB/MCPO projection neurons in PFC-mediated working memory and suggest that pathological alterations in basal forebrain have the potential to contribute to executive dysfunction.

111. **Chronic stress enhanced fear memories are associated with increased amygdala zif268 mRNA expression and are resistant to reconsolidation in an animal model of post traumatic stress disorder.** Hoffman, A.N. University of California Los Angeles Psychology, University of California Los Angeles Neurosurgery, Arizona State University Psychology; Parga, A. Basic Medical Sciences, University of Arizona College of Medicine; Watterson L.R. Arizona State University Psychology; Paode, P.R. Arizona State University Psychology; Nikulina, E.M. Basic Medical Sciences, University of Arizona College of Medicine; Hammer, Jr., R.P. Basic Medical Sciences, University of Arizona College of Medicine; and Conrad C.D. Arizona State University Psychology. The chronically stressed brain may present a vulnerability to develop maladaptive fear-related behaviors in response to a traumatic event. Specifically, chronic stress leads to amygdala hyperresponsivity and dendritic hypertrophy and produces a PTSD-like phenotype that includes exaggerated fear learning following Pavlovian fear conditioning and resistance to extinction. It is unknown whether chronic stress-induced enhanced fear memories are vulnerable to disruption via reconsolidation blockade, as a novel therapeutic approach for attenuating exaggerated fear memories. We used a chronic stress procedure in a rat model (wire mesh restraint for 6h/d/21d) to create a vulnerable brain that leads to a PTSD-like phenotype. We then examined fear behavior following acquisition, reactivation and post-reactivation (i.e., reconsolidation) in a Pavlovian fear conditioning paradigm and the subsequent functional activation of limbic structures using zif268 mRNA measured by in situ hybridization. Chronic stress enhanced amygdala functional activation during fear memory retrieval at reactivation. Moreover, these enhanced fear memories resisted a post reactivation rapamycin challenge to disrupt long term fear memory, and long term memory processing at post-reactivation was also associated with enhanced amygdala (LA and BA), and decreased hippocampal CA1 activation. These results suggest potential challenges for reconsolidation blockade as an effective approach in treating exaggerated fear memories, as in PTSD. Our findings also

support chronic stress manipulations combined with fear conditioning as a useful approach to study a PTSD-like phenotype.

112. **Time course analysis of behavioral heterogeneity in MRL/MpJ lupus-prone and control mice.** Shiue, L. Biology Department Concordia College; Quinlan C. Psychology Department Concordia College; Quincer, E. Biology Department Concordia College; Larson S. Psychology Department Concordia College; Reber J. Mathematics Department Concordia College; Strand K. Biology Department Concordia College. Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disease of unknown etiology that results in severe damage to several tissues including joints, kidneys, heart, lungs and brain. As many as 80% of adults exhibit changes in behavior or cognitive functioning pre- or post-diagnosis with SLE. The MRL/MpJ-Faslpr/J mouse line (MRL/lpr) is one model used to study SLE. MRL/lpr resulted from lymphoproliferation (lpr), a spontaneous autosomal retrotransposon insertional mutation that produces a non-functional variant of the pro-apoptotic cell surface receptor Fas. The congenic MRL/MpJ strain contains a functional transcript for the Fas receptor and develops some lupus-like symptoms much later in life; the MRL/lpr2 strain retains the Fas mutation but compared to MRL/lpr, develops a milder autoimmune phenotype. MRL/lpr animals develop autoantibodies to Smith antigen, nuclear proteins, and native single- and double-stranded DNA. These animals also exhibit changes in cognitive function, emotionality, and motivated behavior associated with autoimmunity; however, researchers report contradictory evidence regarding MRL/lpr performance on tasks measuring these behaviors compared to congenic controls, similar to the wide variety and severity of symptoms reported in humans with SLE. In order to better characterize the MRL model, we compared groups means and analyzed the heterogeneity within groups for peripheral symptoms and behavior and cognitive functioning in 6-, 12-, 18- and 24-wk-old male MRL/lpr, MRL/lpr2, and MRL/MpJ mice. These time points include no, mild, moderate, and severe peripheral symptomology as measured by urinalysis, lymphadenopathy, splenomegaly, and serum antinuclear antibodies. Using univariate analysis of variance, as well as agglomerative and K-means clustering, we found both age and disease effects for all strains, as well as within-strain heterogeneity, on several behavioral measures assessing activity, exploration, memory, anxiety, learning, hedonics, and depressive-like behavior. This work was supported by the Lupus Foundation of Minnesota, the North Central Chapter of the Arthritis Foundation, the National Science Foundation STEP program, and Concordia College.

113. **Relationship of serum complement component C3 with autoimmunity-associated behavior in the MRL/lpr model.** Shiue, L. Biology Department Concordia College; Quinlan, C. Psychology Department Concordia College; Franz, A. Biology Department Concordia College; Strand K. Biology Department Concordia College. Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disease of unknown etiology that results in severe damage to several tissues including joints, kidneys, heart, lungs and brain. Neuropsychiatric SLE (NPSLE) comprises 19 syndromes that include headache, cerebrovasculature disease, seizure, and psychosis. As many as 80% of adults exhibit some NPSLE syndromes, with mood disorders and changes in cognitive functioning among the most prevalent. A compromised blood-brain barrier is concomitant with NPSLE; however, people may experience NPSLE in the absence of systemic disease flairs. The complement cascade comprises several proteins that aid in destroying bacteria and stimulating immune response cells. Inactive complement proteins in the blood are activated by antigens bound to antibodies and initiate a series of cleavage and recruitment steps of other proteins in the cascade. One consequence of complement activation is dilation of blood vessels, which can become leaky. Genome-wide association studies have suggested sequence differences in some complement proteins as risk factors for SLE. There is also contradictory evidence implicating alteration in serum or cerebrospinal fluid levels of the complement protein C3 with NPSLE syndromes. To investigate whether a relationship exists between serum C3 levels and cognitive changes associated with NPSLE, we measured exploration, memory, learning, anxiety, and hedonics in the lupus-prone

MRL/lpr and control strains at presymptomatic to severe lupus-like stages, and quantified serum C3 in these animals using ELISA. The MRL/lpr model contains a nonfunctional pro-apoptotic gene Fas, raises autoantibodies to native DNA, nuclear proteins, and Smith antigen, and is particularly useful for studying the behavioral and cognitive changes associated with autotimmunity. In MRL/lpr and control mice with displaying similar peripheral symptomology, we found differences in C3 serum levels in MRL/lprs compared to controls. Within the MRL/lpr strain, animals displaying passive avoidance learning exhibited higher levels of C3 than those who did not learn (p=.017), and there was a trend of lower C3 levels related to less time spent exploring the center of an open field and greater overall activity. This work was supported by the Lupus Foundation of Minnesota, the North Central Chapter of the Arthritis Foundation, the National Science Foundation STEP program, and Concordia College.

114. **Effects of Chronic Treatment of Corticosterone on Physiological Responses.** 1,2 Ortolani D, 1 Donovan M, 1 Vargas J, 1 Layco E, 1 Onnis G, 1 Hillar C, 2 Spadari RC, 1 Tecott LH. 1 Department of Psychiatry, University of California, San Francisco, CA, USA, 2 Department of Bioscience, Federal University of São Paulo, Santos, SP, Brazil. The HPA axis modulates a diverse array of behavioral and physiological functions through regulation of glucocorticoid release. Chronic elevations of glucocorticoids have been implicated in perturbations of energy balance and affect found in a wide variety of disease syndromes. Objectives: To obtain a detailed quantitative assessment of the impact of elevated corticosterone levels on energy balance and affect, we performed a Home Cage Monitoring (HCM) study. The HCM approach permits continuous automated collection and analysis of high-resolution behavioral datasets, revealing the coordinated regulation of of diverse behaviors. Male C57BL/6J mice were housed in HCM cages, and received either corticosterone (CORT; 100 µg/ml) or vehicle in their drinking water during a 15 day monitoring period. On the 15th treatment day, we examined responses to a novel object placed in the home cages. In accord with previous studies, CORT treatment increased food and water intake, suppressed locomotor activity, and increased adiposity. Lives of mice consist of alternations between inactive states (ISs) occurring at the nest and active states (ASs), during which animals forage and patrol a home range. Within ASs, feeding and drinking events are clustered into bouts. CORT treatment produced substantial changes in circadian patterns of behavior, including opposing effects on DC and LC AS probability. Whereas a DC suppression of AS probability arose from a selective decrease in AS duration, a LC enhancement of AS probability resulted from were driven by selective increases in ingestive bout sizes arising from prolonged bout durations. Additionally, we observed DC-specific suppression of locomotion resulting from both reduction in DC AS probability and reductions in the frequency with which bouts occurred during ASs. In contrast, CORT treatment did not alter locomotor bout properties such as bout size, duration or intensity (speed). We also found CORT treatment to suppress the extent to which animals explored a novel object introduced into the home cage. In sum, our results reveal intricate and highly specific ways that chronic CORT treatment alters components of behavioral patterns and their circadian regulation. A CORT-induced suppression of DC activity is mediated by a selective suppression of AS duration, rather than changes in locomotor bout properties. In contrast, CORT-induced enhancement of feeding arises from a selective increase in feeding bout size driven by prolonged feeding bout durations. These findings are consistent with suppression of the process of within-meal satiation. Moreover, chronic CORT treatment suppressed exploration of a novel object, a finding consistent with an enhancement of anxiety-related behavior. Financial Support. Judith Rose Shea Foundantion, FAPESP.

115. **Improving undergraduate students' knowledge of neuroscience principles and research methods through structured didactics that complement mentored research training.** Laura A. Rabin, Deborah J. Walder, Luz Ospina, John K. Flynn, Susan Y. Chi, Tangeria R. Adams. Department of Psychology, Brooklyn College of The City University of New York. The NSF-funded Neuroscience Research Experiences for Undergraduates (REU) program at Brooklyn College immerses diverse

students in innovative research on clinical, cognitive, and behavioral, neuroscience. Undergraduate research and mentoring experiences are powerful mechanisms to attract and retain students in science majors, promote graduate school aspirations, and serve as a pathway toward careers in science. Our REU program trains 12 students per year and includes 6 hours of structured didactic training in addition to 15-20 hours of mentored laboratory research per week over a 15-week semester. Our weekly journal club was developed to familiarize REU students with the scientific literature in modern neuroscience through learning to select, read, understand, critically analyze, and orally present summaries of original research papers. Our weekly neuroscience seminar was developed to increase students' exposure to and understanding of neuroscience in a manner complementary to their laboratory experience. Overall, these didactics are intended to increase students' exposure to and understanding of neuroscience research and enable students to communicate effectively about their work. The current study presents outcome data related to efficacy of the journal club and neuroscience seminar. REU students (n=24; 58% female, 46% first generation college, and 33% ethical/racial minorities) were evaluated in Week 1 and Week 15 (i.e., before and after participating in the didactics). Students completed four assessments: two questionnaires that assess students' perception of their knowledge of basic neuroscience and research methodology and two multiple choice quizzes that assess students' actual knowledge of basic neuroscience and research methodology. Paired-samples t tests showed statistically significant improvements for the objective and subjective journal club assessments and the objective neuroscience assessment. REU students who underwent our didactic seminars improved in their subjective and objective knowledge over the course the semester. In addition, student feedback supports the idea that the didactics were a worthwhile complement to the lab work, which adds to their overall understanding of, and appreciation for, the scientific method. We discuss the importance of pairing mentored lab-work with seminar-style didactics to enhance students' overall research training experience and we provide suggestions for adapting our seminars to other institutions.

Saturday, June 14

8:00-10:00 **Symposia: Reproductive experiential regulation of cognitive and emotional resilience.**
Chair: Craig H. Kinsley, University of Richmond, USA

Chronic intranasal oxytocin: long-term effects of a reproductive hormone on behavior and neural systems. Bales, K. University of California, Davis. Oxytocin (OT) is a neuropeptide known to be involved in labor induction, milk letdown, orgasm, and the formation of social bonds. It is now being tested as a therapeutic for neurodevelopmental disorders involving social deficits, such as autism spectrum disorders. Effects of long-term exposure to this reproductive hormone are unknown, and quite possibly encompass changes in behavior, central regulation of neuropeptides, and possibly reproductive systems. We will present data from studies of chronic intranasal OT administration in prairie voles, BTBR mice, and titi monkeys. OT was administered daily at a developmental time period approximating the adolescent period in humans. At a dose close to that being used in humans (and at lower doses), chronic intranasal OT had short-term prosocial effects in prairie vole males, but resulted in disrupted pair-bonding in the same males in the long-term. Low doses also increased emotionality in females as measured in the open field test. Prairie vole males displayed lower oxytocin receptor binding in the bed nucleus of the stria terminalis, higher oxytocin receptor binding in the posterior cingulate cortex, and lower production of oxytocin peptide in the paraventricular nucleus. In monkeys, preliminary data from animals of both sexes suggests that exposure to intranasal OT increases the willingness to approach strangers; extremely preliminary findings suggest that sperm transport may be affected in male monkeys treated with OT. In summary, these chronic exposures to OT, a reproductive hormone, may affect both social and emotional behavior, and reproductive systems themselves. This research is supported by HD071998, NIH OD P51OD011107, and the Good Nature Institute.

Catch me if you can: Reproductive experience enhances foraging skills in owl monkeys. Bardi, M., Department of Psychology, Randolph-Macon College, Ashland, VA. Studies on parental behavior in bi-parental species have shown that becoming a parent involves remarkable behavioral changes driven by a combination of neuroendocrine and experiential factors. These parenting-induced modifications extend to brain regions that are not typically associated with parental responses but contribute to enhancements in ancillary parental responses such as foraging efficiency and predator avoidance. For example, reproductively experienced (RE) female rats exhibited improved spatial memory in the dry land maze (DLM) and more exploration in the elevated-plus-maze (EPM) in comparison to nulliparous females (Love et al., 2005). It has also been shown that RE females had enhanced foraging behavior, likely as an evolutionary mechanism to increase the likelihood of pup survival (Lambert et al., 2004). More recently we aimed to test if similar effects can be found in a bi-parental primate species, the owl monkey (Aouts spp.). On the basis of previous studies on several primate species showing how the dramatic physiologic changes occurring across parturition may act to help the mother cope with the additional challenges imposed by the newborn, it was hypothesized that adaptive behavioral and physiological responses would be observed in RE male and female owl monkeys in comparison of their non-RE counterparts. We also hypothesized that RE would enhance their natural foraging skills (insect-foraging). To assess their cognitive skills and coping flexibility, a foraging strategy task, including a set of novel objects marked with different symbols representing varying food rewards, was introduced to the animals. To assess endocrinological responses, urine samples were collected and assayed for cortisol and dehydroepiandrosterone (DHEA) to determine physiological measures of emotional regulation in parental and non-parental owl monkeys. To record their natural propensities in insect prey, camera-traps were installed at night when the species is active, and the frequency of successful attempts was compared in the two groups. Corroborating previous research demonstrating adaptive modifications in foraging efficiency and emotional responses in reproductively experienced rodents, in this presentation I will provide evidence that ancillary parental modifications are widespread in mammals, very likely as a homologous trait selected to increase the probability of both infant and parent survival, and the successful passage of the parents' genes.

Pregnancy/reproductive experience: a neuro-developmental epoch takes its place alongside sexual differentiation and puberty. Kinsley, C. Mothers are made, not born. In the maternal mammal, pregnancy and its attendant hormonal fluctuations render the brain both motivated toward, and responsive to, the female's offspring. She experiences a most significant and transformative event during this conversion from virgin to first-time mother, from nulliparity to primiparity. Along with the creation of a litter bearing half of her genes, the episode graphically demonstrates the inherent plasticity of the female brain, and represents a developmental epoch as significant as sexual differentiation and puberty before it. "M" may be "for the many things she does," but modifications in her behavioral capacity occur because of the multitude of (likely permanent) neural changes taking place. What was once an organism largely self-directed, becomes one focused on the care and well-being of its offspring. For the female rat, provisioning her nest and its inhabitants takes precedence, where finding and acquiring food or subduing prey is integral to offspring surviving. The obstacles arrayed against successful reproduction are formidable. We are finding that the maternal brain, with its inherent plasticity, provides the female with the capacity to respond with an even richer and enhanced behavioral repertoire. Artemis was the goddess of childbirth and the hunt, mother and provider. Maternal behavior in the rat may incorporate the complementary elements that the early Greeks envisioned, and involve many different brain regions. That is, a mother is anything but one-dimensional; likewise, maternal behavior encompasses many facets beyond direct care of young. For instance, consider the many new behaviors a female must perform once her young are present. Formerly unfamiliar activities are required of the mother, including behaviors such as retrieving wayward pups, grouping and crouching-over, and licking/physically stimulating the offspring, and protecting them against predators. Further, building onto and enhancing existing behavioral repertoires such as nest building, foraging and aggression would be expected to happen, too. In order to tend to her nest and young, the new mother must strike a Faustian bargain: leave the relative safety of the nest and her helpless offspring to forage for food and resources where predators await both mother and young, or remain ensconced, ensuring a slow and inexorable fate. Enter maternal nervous system adaptation: behavioral solutions ensue, leading to greater survivability.

Epigenetic regulation of maternal learning. Stolzenberg, D. University of California Davis. Experiences that occur during development have enduring effects on brain and behavior, which persist across the lifetime of an organism. However, experiences that occur after critical developmental windows close can also re-shape the brain and change behavior. Motherhood is one such experience, gained in adulthood, that has robust effects on brain and behavior. The transition into motherhood is typically precipitated by the hormonal events of pregnancy and birth, which decrease anxiety and increase attraction to infants. At birth, rodent mothers are so highly motivated to interact with their offspring that they will traverse an anxiogenic, novel environment (such as a novel T-maze) or learn to press a lever to interact with pups. This experience of becoming a mother results in a sustained sensitivity toward infants that functions to ensure the mother will successfully handle the demands of motherhood and continue to provide maternal care. The medial preoptic area (MPOA) of the hypothalamus, which plays a critical role in this process, integrates hormonal and pup-related information from all sensory modalities and regulates maternal behavior responses. A major research theme has been to understand mechanisms through which genetic and epigenetic modifications induce phenotypic plasticity in MPOA neurons, which support functional changes in maternal responding. In particular, we have explored the hypothesis that chromatin modifications mediate effects of maternal experience on maternal care by potentiating the ability of infant stimuli to activate the neural circuit that regulates maternal behavior. Chromatin is the complex of DNA compactly coiled around histone proteins. The post-translational modifications of histones by histone acetyltransferase (HAT) enzymes leave "epigenetic marks" that exist above the level of the genome and control gene expression. In support of the idea that epigenetic modifications mediate plastic changes in maternal responding, increasing HAT activity reduces the amount of maternal experience required to sustain maternal care long-term. Further, the consolidation of maternal experience seems to involve the recruitment of a HAT to gene promoters and stable changes in gene expression, which are

associated with long-term increases in maternal responsiveness. Thus, the experience of motherhood may be regulated by epigenetic mechanisms.

8:00-10:00 **Symposia: Diet, behaviour, and immunity across the lifespan.** Chair: Stephen Kent, La Trobe University, Australia.

Diet affects executive function: Effects across the lifespan. Teresa M. Reyes. There is a growing appreciation for the role that diet plays in optimizing brain development, and subsequent behavior. Suboptimal diets during critical developmental periods, such as pregnancy and adolescence, can lead to long-term adverse neurobehavioral outcomes. In this presentation, data will be presented that demonstrate vulnerability at the level of the prefrontal cortex, with effects on executive function (attention and impulsivity). Work in our lab studies suboptimal prenatal development by feeding mouse dams a diet low in protein or high in fat, which results in pups that are either small or large for gestational age, respectively (SGA and LGA). When tested in the 5 choice serial reaction time task, SGA pups display inattention, while LGA pups show impulsivity. Potential molecular mechanisms linking prenatal diet to executive function deficits will be discussed.

The role of microglia in perinatal diet's programming effects on neuroimmune function. Sominsky L; Spencer SJ. Obesity is characterized by a chronic low-grade inflammation. At the level of the hypothalamus, this inflammation can lead to a disruption of the pathways regulating feeding and metabolism and a resistance to satiety signalling from leptin and insulin. Although hypothalamic inflammation can be influenced by diet at any stage of life, the early life nutritional environment is likely to be particularly important because of its potential to influence how central immune cells mature. We have seen rats suckled in small litters (of 4; SL) develop an overweight phenotype, compared with those suckled in control litters (of 12; CL), that is evident by as early as postnatal day (P) 7 and persists into adulthood. These SL rats also have exacerbated neuroimmune responses to an immune challenge with lipopolysaccharide (LPS). This exacerbated pro-inflammatory response may be partly due to alterations in the normal maturation of microglia within the young brains of neonatally overfed rats, by encouraging the microglia to remain in a 'primed' or sensitized state that can contribute to a basal pro-inflammatory profile. We thus examined inflammatory profiles, including microglial proliferation and morphology, in rats suckled in CL or SL at P7 and P14. Neonatally overfed rats have more microglia in the paraventricular nucleus, and other regions of the hypothalamus, accompanied by changes in the pro-inflammatory profile. These findings suggest neonatal overfeeding can alter microglial maturation, potentially contributing to exacerbated central responses to an immune challenge.

Mum's the word: Understanding the role of maternal inflammation in elevating the risk of offspring neuroendocrine disorders. Jasoni C, Kim D, Sanders T Department of Anatomy, Centre for Neuroendocrinology, University of Otago, Dunedin. A mother's obesity during pregnancy is well-recognised for its ability to elevate her offspring's risk of obesity and the metabolic syndrome. Because the physiology of the mother and her offspring interact most intimately during gestation, we have been characterising the changes that take place to the fetal brain during its development in an obese mother, with particular focus on the regions of the brain that regulate feeding behaviors later in life. Female C57B/6J mice were fed a high-fat diet (45% kcal from fat) for 6 weeks beginning one week after weaning. This protocol results in >30% increase in body weight compared to control-fed age-matched females, and offspring show elevated body weight and blood glucose when fed a high-fat diet. At birth, we observed significant anatomical changes in neuronal connectivity between the arcuate (ARC) and paraventricular nuclei of the hypothalamus, two interconnected brain areas that regulate body weight. We then used NextGen sequencing to determine whether anatomical changes could be accounted for by altered developmental gene expression. At gestational day 17.5 (GD17.5), the ARC of fetuses developing in obese mothers showed altered expression of developmental genes controlling axon growth and guidance. Several of these genes encode axon guidance receptors and were expressed specifically by ARC neurons that control body weight. Other genes were expressed in nearby regions where

their products could influence growth of ARC neuronal processes. To understand the cellular mechanisms linking maternal obesity to altered developmental gene expression, we have investigated a possible role for cytokines. We have used a multiplex cytokine assay to identify significantly elevated interleukin-1B and interleukin-6 (IL6) in the fetal circulation at GD17.5. Treatment of ARC explants with IL6 significantly reduced axon growth in vitro, and this was accompanied by altered gene expression that mimicked that seen in vivo. Taken together these observations suggest that elevated inflammation in the brains of fetuses developing in obese mothers may act to alter developmental gene expression and thereby derail normal formation of the neural circuitry that controls body weight later in life. Understanding how the prenatal environment has an impact on later life health and disease is one of the first steps toward developing strategies for ensuring a healthy start to life and life-long health for the babies of obese mothers.

The interleukin 18 system in the central regulation of feeding. Bruno Conti, The Scripps Research Institute. Cytokines produced during infection or diseases can affect energy homeostasis by reducing nutrient intake and/or increasing energy expenditure. The pro-inflammatory cytokine Interleukin 18 (IL-18) can be produced centrally by microglial cells during inflammation, and by neurons of the medial habenula as well as by ependymal cells during stress. IL-18 acts trough a heterodimer receptor comprised of a subunit alpha (IL-18Rα) required for binding and a subunit beta (IL-18Rβ) necessary for activation of signal transduction. Differential promoter usage and alternative splicing can also originate truncated isoforms of IL-18Rα and β believed to be decoy and serve to the negative regulation of IL-18 action. In addition, a soluble IL-18 binding protein can prevent IL-18 to engage IL-18Rα. All members of the IL-18R are expressed in neurons throughout the brain with high levels in the hypothalamus, where IL-18Rα and β were found in several areas including the arcuate (ARC), lateral (LH), ventromedial (VMN), paraventricular (PVN) and dorso-medial (DMN) nuclei. Mice deficient in IL-18 (Il18-/-) or the receptor alpha subunit (Il18Rα-/-) overeat as young adults and then rapidly develop maturity-onset obesity. Conversely, central IL-18 administration in the third ventricle was anorexigenic, suppressing food intake and weight regain in hungry mice. Collectively, these findings indicate that IL-18 can act as central modulator of energy balance and may do so by directly acting on hypothalamic neurons that regulate feeding.

Calorie restriction attenuates lipopolysaccharide-induced microglial activation in discrete regions of the hypothalamus. Matthew W. Hale, Morgan E. Radler, Stephen Kent, School of Psychological Science, La Trobe Univeristy, 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. CR also suppresses microglial activation following cortical injury and aging. We previously demonstrated that CR attenuates lipopolysaccharide (LPS)-induced fever and shifts hypothalamic signaling pathways to an anti-inflammatory bias; however, the effects of CR on LPS-induced microglial activation remain largely unexplored. The current study investigated regional changes in LPS-induced microglial activation in mice exposed to 50% CR for 28 days. Immunohistochemistry was conducted to examine changes in ionized calcium-binding adapter molecule-1 (Iba1), a protein constitutively expressed by microglia, in a total of 27 brain regions involved in immunity, stress, and/or thermoregulation. Exposure to CR attenuated LPS-induced fever, and LPS-induced microglial activation in a subset of regions: the arcuate nucleus (ARC) and ventromedial nucleus of the hypothalamus (VMH) and the subfornical organ (SFO). Microglial activation in the ARC and VMH was positively correlated with body temperature. These data suggest that CR exerts effects on regionally specific populations of microglia; particularly, in appetite-sensing regions of the hypothalamus, and/or regions lacking a complete blood brain barrier, possibly through altered pro- and anti-inflammatory signaling in these regions.

10:30-11:30 **Presidential Lecture:** Food on the brain – Why is obesity a 21st century problem? M. J. Morris

Food on the brain – Why is obesity a 21st century problem? Margaret J Morris School of Medical Sciences, UNSW, Australia. Changes in food composition and availability have contributed to the dramatic increase in obesity over the past 30-40 years. The brain plays a critical role in regulating energy balance. We have examined neurochemical changes in the brain in animal models during the development of obesity, and the mechanisms underlying the intergenerational transmission of obesity. Maternal obesity leads to "programming" of the neural circuitry involved in appetite regulation. Our work shows maternal obesity alters hypothalamic expression of key appetite regulators, from as early as day one of life. Using rats, we found exercise in the offspring of obese mothers, regardless of their postweaning diet, improves metabolic profile. Using western foods high in fat and sugar, we showed that palatable diet leads to more 'snacking', relative to lean rats, and our obese rats moved less than lean rats. Importantly, withdrawal of the palatable diet led to a stress-like response. Impairments in cognitive function have been associated with obesity. As little as one week of exposure to a high fat, high sugar diet selectively impaired some types of learning in the rat. Excess sugar alone had similar effects, and both diets were linked to increased inflammatory markers in the hippocampus, a critical region involved in memory. Obesity related inflammatory changes have been described in the human CNS. Ongoing work aims to test interventions to prevent or reverse the learning deficits. These data have implications for minimizing harm caused by unhealthy eating.

3:30-5:30 **Symposia: Sex-differences in developmental psychopathologies: An animal model perspective.** Chair: Ina Weiner, Tel-Aviv University, Israel

Sex-specific behavioral and molecular deficits in 'two hit' models of developmental stress: role of brain-derived neurotrophic factor. Van den Buuse M (1,2); Klug M (1); Hill R (1); (1) Florey Institute for Neuroscience and Mental Health, University of Melbourne, Melbourne, Australia; (2) School of Psychological Science, La Trobe University, Melbourne, Australia. Schizophrenia and other psychiatric illnesses are likely caused by a combination of genetic and environmental factors. Brain-derived neurotrophic factor (BDNF) is involved in brain development and plasticity and is implicated in schizophrenia and depression. To model 'two hit' gene-environment interactions and the involvement of BDNF, we investigated the long-term effects of corticosterone treatment (CORT) to simulate chronic stress. We previously showed that this treatment results in deficits in spatial memory in a Y-maze task in male BDNF heterozygous mice, but not wildtype controls (Klug et al., Neurobiol Dis 2012). In male maternally-separated rats, CORT induced similar deficits. In both models, there were no CORT effects in females; however these animals displayed anhedonia-like behaviour which was not observed in males. Male/female-specific behavioral changes in maternally-separated rats were correlated with differential effects on exon-specific BDNF expression in the dorsal hippocampus, prelimbic cortex and nucleus accumbens between the sexes. Moreover, these 'two hit' effects were accompanied by sex-specific alterations in regional NMDA receptor subunit expression. These studies suggest that developmental stress effects may be modulated by estrogen as it interacts with BDNF/TrkB gene expression and signaling. Indeed, in separate studies, the adolescent/young adult developmental trajectory of BDNF signaling in different brain regions, such as the frontal cortex and dorsal hippocampus, was markedly different between male and female mice and sensitive to altered circulating levels of these sex hormones. Furthermore, in animal and human studies we observed differential effects of estrogen and testosterone in behavioral paradigms with relevance to schizophrenia, such as prepulse inhibition (PPI). In conclusion 'two hit' models of developmental stress reveal sex-specific vulnerability to behavioral and molecular deficits. We are currently investigating the 'two hit' effects of BDNF deficiency and drugs of abuse, such as cannabis and methamphetamine. We have also investigated CORT effects in BDNF heterozygous rats and results will be shown. Overall, these studies could be relevant for our understanding of sex differences in psychiatric illnesses and potential treatments based on sex steroid hormones.

Sexually dimorphic and developmental effects of maternal separation on prefrontal cortex, behavior and inflammation in rats. Brenhouse H.C., Holland F.H., Golan N., Backus T., Northeastern University, Boston MA. Early adverse experience plays an important role in psychopathology by altering memory and motivational processes. These effects often manifest in adolescence, in parallel with the later-developing prefrontal cortex (PFC). For example, we have observed that ELS in males leads to a decrease in PFC inhibitory interneurons that express the protein parvalbumin in adolescence, but not earlier. The timeline of PFC development can differ between males and females, and most neuropsychiatric disorders that involve PFC dysfunction exhibit sex bias in their presentation. However, little is known mechanistically about whether early life stress affects males and females differently. Notably, growing evidence suggests that neuroinflammation interacts with development to mediate the emergence of dysfunction after ELS, and therefore is a promising target of investigation. Here, we will discuss experiments in which male and female rats were subjected to early life stress (ELS) using maternal separation or were facility reared from postnatal day (P)2-20. Peripheral and central inflammatory markers were measured along with PFC parvalbumin, dendritic morphology, and several behaviors over development. Adolescent behavioral deficits were correlated with early circulating pro-inflammatory markers preferentially in males, while females displayed earlier behavioral dysfunction and significant changes in PFC dendritic morphology. We will discuss emerging evidence that ELS affects males and females through different developmental mechanisms, which manifest behaviorally at different time-points.

Immune activation in lactating mothers produces long-term structural brain and behavioral abnormalities that are distinct in male and female sucklings: A novel neurodevelopmental model of sex-biased psychopathology. Ina Weiner, Schools of Psychological Sciences and Neuroscience, Tel-Aviv University, Tel-Aviv, Israel. Sex bias is a ubiquitous characteristic of adult onset neuropsychiatric disorders including schizophrenia and affective disorders, suggesting that sex is an important susceptibility factor, and should be considered in the etiology of such disorders. Model rodents with developmental disruptions can be informative for exploring the role of sex in disease vulnerability. Because altered neuroimmune mechanisms play a role in schizophrenia and affective disorders, early-life (prenatal or postnatal) infection/inflammation is widely used to produce relevant behavioral and brain endophenotypes, but consistent with male bias in neuroscience, most studies assess only male offspring. Here we used lactation as a vehicle for exposing 4-day old female and male neonates to the viral mimic polyriboinosinic-polyribocytidylic acid (poly-I:C), and assessed both sexes for the presence of depression-, mania-, and schizophrenia- phenotypic behaviors and brain volumetric changes. Immune activation in lactating dams led to sexually dimorphic behavioral endophenotypes in adulthood, with male but not female offspring exhibiting cognitive inflexibility (persistent latent inhibition and slow reversal) and hypodopaminergia, and female but not male offspring exhibiting affective deficit (increased immobility in FST and reduced saccharine preference) and hyperdominergia, consistent with sex bias in SCZ and affective disorders. Tracing the neurodevelopmental and behavioral trajectories between adolescence and adulthood revealed that lactational poly-I:C led to sex-independent region- and maturation specific volumetric reductions in the hippocampus, prefrontal cortex and striatum that predated the sex-specific behavioral abnormalities which emerged at the same time in young adulthood. Our finding that the same neurodevelopmental insult led to schizophrenia- and depression -relevant "symptoms" is in line with the recently emphasized notion that risk factors are transdiagnostic. Furthermore, they show that sex can transform some common neurodevelopmental etiologies into distinct psychopathologies, in line with the notion that sex may constitute an important susceptibility factor for the development of psychopathologies of developmental origin. It remains to be determined which aspects of early insults and at which developmental stage/s, interact with the sex of the brain to produce distinct psychopathologies.

Early-life modulation of Cav1.2 induces sex-specific resiliency to depression. Michal Arad a, J. Michael Bowers b, Margaret M. McCarthy a,b,c,d, Todd D. Gould a,c,d,e a Department of Psychiatry, b Departments of Pharmacology, c Program in Neuroscience, d Department of Physiology e Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD 21201. Genetic studies have

associated polymorphisms in the CACNA1C gene with a mood disorder diagnosis. CACNA1C codes for Cav1.2, which is an L-type voltage-gated calcium channel (LTVGCC) alpha-1 subunit. Recently, we reported that Cacna1c haploinsufficiency in the mouse alters resilience to depression-related behaviors in a sex-dependent manner. Given that male and female Cacna1c haploinsufficient mice share reduced levels of Cav1.2 LTVGCC, but females showed greater resiliency than males to depression-like symptoms, our aim was to assess whether the interaction between the sex of the brain and Cav1.2 LTVGCC levels during a sensitive period for sexual differentiation of the brain may account for the development of sex-specific depression-like behavior. To that end, we used two early life manipulations: 1) Cacna1c haploinsufficient and wild type (WT) female mice (C57BL/6J background) were exposed to hormonal masculinization of the brain by a single injection of testosterone (0 or 100µg/mouse) on postnatal day (PND)-0. 2) Male and female WT mice received a bilateral intracerebroventricular injection of nimodipine (Cav1.2 LTVGCC blocker; 0 or 0.25µg/0.25µl/side) on PND-0. At adulthood (>PND-77), all mice were tested in the Forced Swim Test and Learned Helplessness procedures which assess depression-like behaviors. Resiliency to depression in Cacna1c haploinsufficient females was attenuated in females neonatally exposed to testosterone. Neonatal blockade of Cav1.2 LTVGCC by administration of nimodipine led to reduce depression-like behavior in WT females, but not in WT males. Furthermore, neonatal intracerebroventricular administration of nimodipine modulated CREB phosphorylation (using Western blot) in the frontal cortex, hippocampus and amygdala of female but not male neonates. These findings provide further support for the sex-dependent role of LTVGCC in the development of depression, suggesting that neonatal changes in activity of LTVGCC alter mood disorder related behaviors selectively in females. As women are at greater risk of depression, our novel neurodevelopmental model may be useful to further understand the role of Cav1.2 LTVGCC in the development of sex-biased mood disorders.

3:30-5:30 **Symposia: Traumatic brain injury: Laboratory and clinical perspectives.** Chairs: A. E. Kline; C. O. Bondi

Contemporary Laboratory Models of Traumatic Brain Injury. C. E. Dixon, Pittsburgh VA Healthcare System and University of Pittsburgh. Traumatic brain injury can result in the disturbance of cognitive, behavioral, emotional, and physical functioning. Residual cognitive disturbance remains a significant concern of persons with concussive to severe TBI. Experimental models of TBI have been developed to study injury biomechanics, discover pathological mechanisms, and develop therapies with the goal of reducing TBI-induced human suffering. My talk will describe contemporary animal models of TBI with a focus on their neurobehavioral and neuropathological outcomes. Models relevant to sports- and military-related TBI will also be discussed.

Social behavior after injury to the developing brain. Semple BD (1,2), Sam PN (1), Gimlin K (1), Schenk AK (3) and Noble-Haeusslein LJ (1,4). 1=Departments of Neurological Surgery and 4=Physical Therapy and Rehabilitation, University of California San Francisco, CA, USA. 2=Department of Medicine (Royal Melbourne Hospital), Melbourne Brain Centre, University of Melbourne, Parkville, VIC, Australia. 3=Department of Physics, Randolph College, Lynchburg, VA. Accumulating evidence suggests that traumatic brain injury (TBI) at a young age may have adverse consequences on the development of social behaviors. However, the trajectory and mechanisms underlying social dysfunction after injury are unclear. We hypothesized that a young brain may show particular vulnerability to such deficits, given the ongoing development of normal social behaviors throughout childhood and adolescence. In these studies, a moderate-to-severe TBI was induced by controlled cortical impact to male mice at either post-natal day 21 or 35, to model a toddler or adolescent-aged human, respectively. We demonstrate that changes in social investigation, socio-sexual behaviors and social communication result from injury at a younger age, while adolescent brain-injured mice show considerable resilience to social deficits. Further, the manifestation of social dysfunction was found to be dependent upon several other variables including time post-injury, injury severity, and the location of the impact. Together, these studies highlight the unique vulnerability of the developing brain to long-term social

dysfunction after TBI. Implementation of standardized assays for social behavior in preclinical TBI studies, particularly in the context of the immature brain, should be encouraged.

Old dog, new tricks: the attentional set-shifting test as a novel cognitive behavioral task after controlled cortical impact injury. Corina O. Bondi, Physical Medicine and Rehabilitation, Safar Center for Resuscitation Research, Center for Neuroscience, and Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA. Cognitive impairment associated with prefrontal cortical dysfunction is a major component of disability in traumatic brain injury (TBI) survivors. Specifically, deficits of cognitive flexibility and attentional set-shifting are present across all levels of injury severity. While alterations in spatial learning have been extensively described in experimental models of TBI, studies investigating more complex cognitive deficits are relatively scarce. To address this important issue, the aim of this preclinical study was to first evaluate the effect of a controlled cortical impact (CCI) injury on executive function and behavioral flexibility performance as assessed using the well-validated attentional set-shifting test (AST). The AST involves a series of increasingly difficult discriminative tasks to obtain food reward, including simple and compound discriminations, stimulus reversals, and intra- and extradimensional (ED) shifts. Furthermore, environmental enrichment (EE) was employed as a therapeutic approach of preclinical rehabilitation aiming to restore cognitive performance post-injury, given a considerable literature showing improvements in behavioral and histological outcome after brain trauma.

Standard vs. Enriched Housing after Traumatic Brain Injury: When Less is Not More. Anthony E. Kline, University of Pittsburgh, Department of Physical Medicine & Rehabilitation, Safar Center for Resuscitation Center, Center for Neuroscience. Environmental enrichment (EE) is a complex living milieu that has been shown to enhance functional recovery vs. standard (STD) housing after experimental traumatic brain injury (TBI) and therefore may be considered a rodent correlate of rehabilitation. However, the typical EE paradigm consists of immediate and continuous exposure to enrichment after TBI, which is inconsistent with the timing parameters in clinical rehabilitation where patients typically will not begin rehabilitation until days after injury and then will receive therapy for only a few hours per day. The goal of this presentation is to discuss the results of studies designed to more accurately mimic the clinical scenario.

Fact or Fiction: An Evidence-Based Approach to Sports-related Concussion. Christopher C. Giza. Mild traumatic brain injury (TBI) or concussion is an increasing concern, particularly in the setting of repetitive injuries as seen in sports and the military. However, information generally available in the lay press offers a different understanding than careful review of the existing objective evidence. Here we will take a translational perspective, linking what is known about the pathophysiology of mild TBI with the existing clinical literature. Topics covered will include the epidemiology of sports-related concussion (SRC), tools to assess SRC, the risk of repeat injury, risk of prolonged recovery, treatments for SRC and the linkage between repeated mTBI/SRC and chronic neurodegeneration. Existing data suggest that females as well as males sustain SRCs, and indeed may be more vulnerable. No single test is available to diagnose concussion, so current recommendations are to use a multi-tiered approach to assessment. There are identified risk factors both for sustaining repeat SRC as well as for experiencing prolonged recovery. The proper management of SRC holds many controversies, but protection from contact-risk and cognitive restructuring have evidence to support their use. Other interventions, including complete cognitive and physical rest, controlled exercise, pharmacotherapy and nutritional supplements are lacking definitive data at this time. Finally, a discussion of the different relationships between repeat SRC, persistent cognitive impairment and chronic neurodegeneration will outline the current state of the evidence, as well as delineate areas needed for future investigation.

IBNS CALL FOR SYMPOSIA and SATELLITE PROPOSALS

The Program Committee is now soliciting proposals for symposia and satellites for the next Annual Meeting of the International Behavioral Neuroscience Society to be held at the Fairmont Empress Hotel, Victoria, BC, Canada, June 2-7, 2015. We look forward to another scientifically excellent conference in an exciting venue.

A typical symposium includes four (4) speakers and is scheduled for two (2) hours. The time and date of symposia are set by the Program Committee. IMPORTANT: In addition to standard symposium proposals, we elicit proposals using innovative formats, for which 2-hour slots will also be available.

All symposia proposals should include a title, the name of the chairperson(s), a substantive description of the topic and proposed talks, the list of speakers, their affiliations and email address, and tentative titles of their talks. Costs of attending the meeting are not financially supported by the IBNS. Each organizer and speaker is expected to cover their own fees.

Satellites are structured and financed by the organizers. Satellite meetings may be held either prior to or after the IBNS meeting dates. Satellite proposals should also include the anticipated location and plans for financing. All proposals are reviewed by the Program Committee and then submitted to the IBNS Council for consideration.

The deadline for priority consideration of symposium proposals is September 15, 2014. Details for submission of proposals will be available on the IBNS website.

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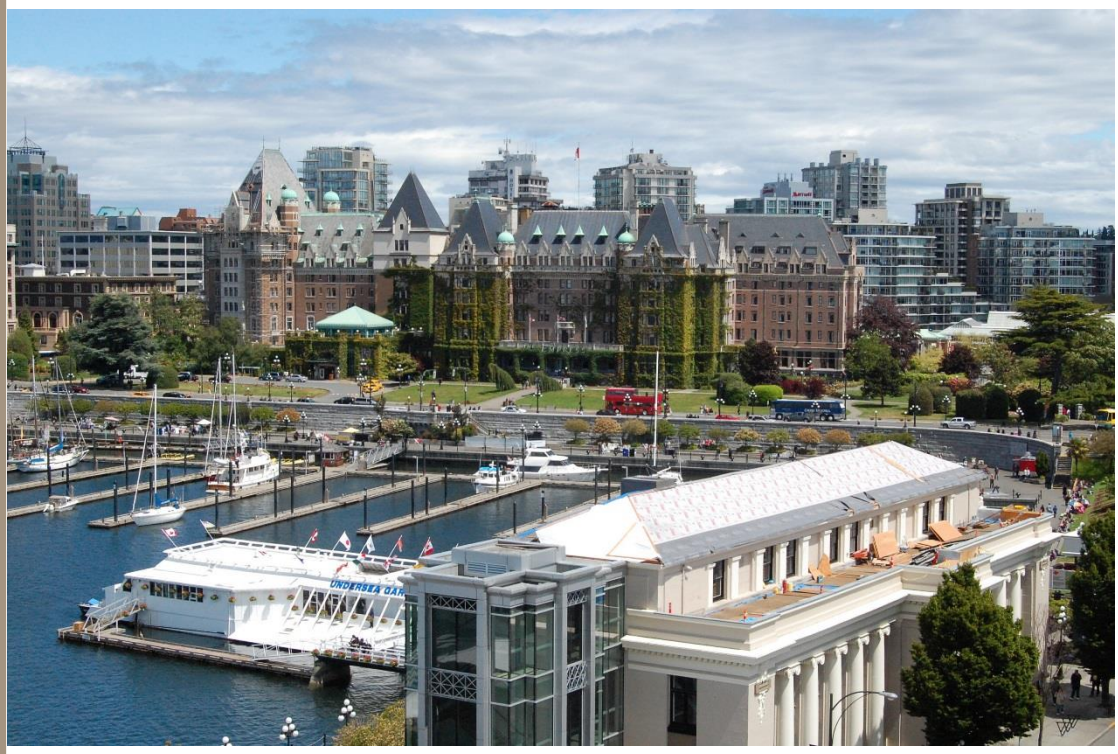

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Summary Program

Tuesday, June 10

11:00-1:00 **Council Meeting** - *Willows*
2:30-4:30 **Student Social** (for students & post-docs) - *Veranda F*
4:30-6:00 **Registration -** *Foyer Cherry Lounge*
6:00-9:00 **Welcome to Vegas Reception -** *Cherry Lounge*

Wednesday, June 11

7:30-8:00 **Exhibitor Displays - Coffee/Tea Break** - *Pavilion Ballroom*
8:00-10:00 **Symposia: The importance of the alleviation of negative affective states and cognitive impairments in animal models of nicotine dependence**. Chair: F. Scott Hall – *Charleston AF*
8:00-10:00 **Symposia: Brains in the City: Neurobiological effects of urbanization.** Chair: Kelly Lambert – *Charleston BCDE*
10:00-10:20 **Exhibitor Displays - Coffee/Tea Break -** *Pavilion Ballroom*
10:20-10:30 **Presidential Welcome** – Brain Safety Initiative
10:30-11:30 **Keynote Speaker.** Cross-species translational studies of bipolar disorder. M. Geyer – *Charleston BCDE*
11:30-1:00 **Lunch/Networking Break** (meals not provided)
1:00-3:00 **Young Investigator Travel Award Data Blitz** – *Charleston BCDE*
3:00-3:30 **Exhibitor Displays - Coffee/Tea Break -** *Pavilion Ballroom*
3:30-5:30 **Symposia: That's why they call it gambling: Neural mechanisms regulating risk/reward decision making.** Chair: Stan B. Floresco – *Charleston BCDE*
3:30-5:30 **Symposia: Behavioral endpoints in drug discovery: What does the pharmaceutical industry need?** Chair: Sophie Dix – *Charleston AF*
5:30-7:30 **Poster Session 1** – *Pavilion Ballroom*

Thursday, June 12

7:30-8:00 **Exhibitor Displays - Coffee/Tea Break** - *Pavilion Ballroom*
8:00-10:00 **Symposia: Warm feelings, warm thoughts: Thermosensation, emotional behavior, and mental health.** Chair: Christopher A. Lowry – *Charleston AF*
8:00-10:00 **Symposia: Chronic stress and brain plasticity: Contrasting mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders.** Chair: Serge Campeau – *Charleston BCDE*
10:00-10:30 **Exhibitor Displays - Coffee/Tea Break** – *Pavilion Ballroom*
10:30-11:30 **Bench-to-Bedside Lecture.** Coming to our senses: Implications of embodiment for the pathogenesis and treatment of major depression. C. L. Raison – *Charleston BCDE*
11:30-12:15 **Publishing Workshop.** Toby Charkin, Elsevier. Panelists: Stephen Kent, Jared Young, Mikhail Pletnikov – *Charleston AF*
12:30-2:00 **Meet the Professionals** (meals not provided) **–** *meet in Pavilion Ballroom*
12:15-3:00 **Lunch/Networking Break** (meals not provided)
3:00-3:30 **Exhibitor Displays - Coffee/Tea Break** – *Pavilion Ballroom*
3:30-5:30 **Symposia: The role of CRF and CRF receptor expression in the progression and pathology of major depressive disorder.** Chairs: Marion Rivalan and R. Parrish Waters, Cliff Summers – *Charleston BCDE*
3:30-5:30 **Oral Session 1: Addiction** – *Charleston AF*
5:30-7:30 **Poster Session 2**– *Pavilion Ballroom*

Friday, June 13

7:30-8:00 **Exhibitor Displays - Coffee/Tea Break** - *Pavilion Ballroom*
8:00-10:00 **Symposia: Current advances in animal models of neurodevelopmental disorder**s. Chair: Mu Yang – *Charleston BCDE*
8:00-10:00 **Symposia: Deep brain stimulation of the basal ganglia nuclei: Animal and human studies.** Chair: Claudio Da Cunha – *Charleston AF*
10:00-10:30 **Exhibitor Displays - Coffee/Tea Break -** *Pavilion Ballroom*
10:30-11:30 **Keynote Speaker.** Closing the translational gap between mutant mouse models and the clinical reality of psychotic illness. J. L. Waddington – *Charleston BCDE*
11:30-1:00 **Lunch/Networking Break** (meals not provided)
1:00-2:45 **Oral Session 2. Disease** – *Charleston BCDE*
1:00-2:45 **Oral Session 3: Mechanisms** – *Charleston AF*
2:45-3:30 **Exhibitor Displays - Coffee/Tea Break** – *Pavilion Ballroom*
3:30-5:30 **Symposia: Neural mechanism of regulation and disruption of motivational behaviors.** Chairs: Hidehiko Takahashi, Christelle Baunez – *Charleston BCDE*
3:30-5:30 **Symposia: Scents that matter – from olfactory stimuli to genes, behaviors and beyond**. Chairs: M. Fendt, Y. Kiyokawa – *Charleston AF*
5:30-7:30 **Poster Session 3**– *Pavilion Ballroom*

Saturday, June 14

7:30-8:00 **Exhibitor Displays - Coffee/Tea Break** - *Pavilion Ballroom*
8:00-10:00 **Symposia: Reproductive experiential regulation of cognitive and emotional resilience.** Chair: Craig H. Kinsley – *Charleston AF*
8:00-10:00 **Symposia: Diet, behaviour, and immunity across the lifespan.** Chair: Stephen Kent – *Charleston BCDE*
10:00-10:30 **Exhibitor Displays - Coffee/Tea Break** – *Pavilion Ballroom*
10:30 -11:30 **Presidential Lecture**: Food on the brain – Why is obesity a 21st century problem? M. J. Morris – *Charleston BCDE*
11:30-3:00 **Lunch/Networking Break** (meals not provided)
3:00-3:30 **Coffee/Tea Break** – *Pavilion Ballroom*
3:30-5:30 **Symposia: Sex-differences in developmental psychopathologies: An animal model perspective.** Chair: I. Weiner – *Charleston AF*
3:30-5:30 **Symposia: Traumatic brain injury: Laboratory and clinical perspectives.** Chairs: Anthony E. Kline; Corina O. Bondi – *Charleston BCDE*
5:30-6:00 **Business Meeting** – Open to all Members – *Charleston BCDE*
6:30-1:00 **Awards Banquet –** Pavilion Ballroom

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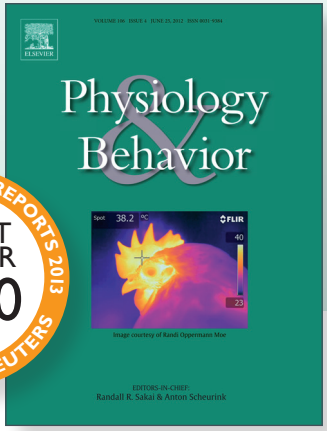

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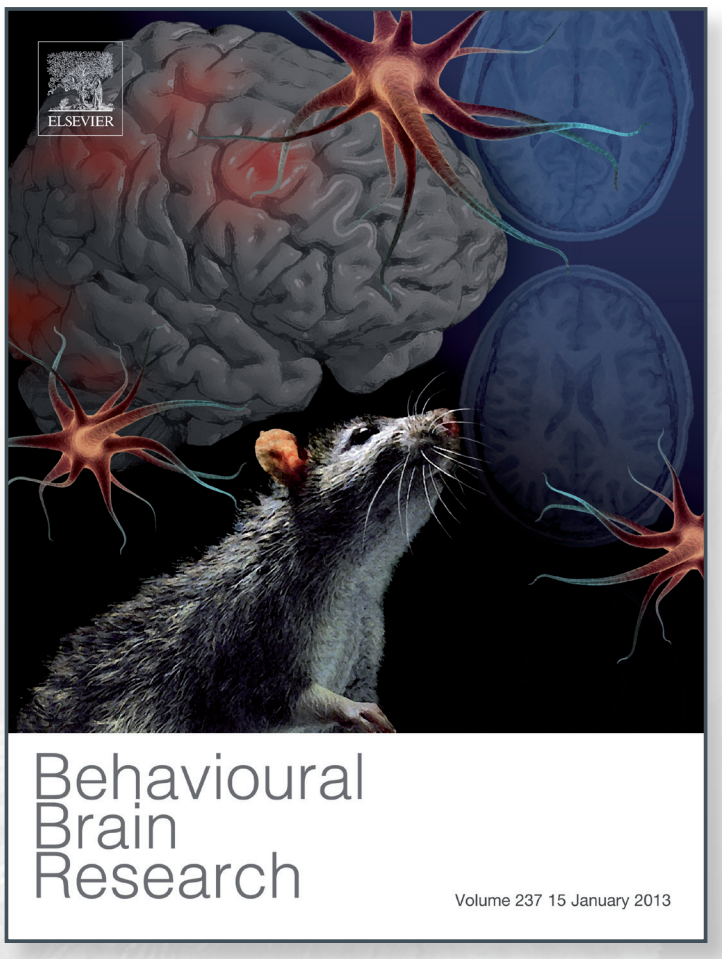

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