International Behavioral Neuroscience Society

Annual Meeting
Program and Abstracts

Malahide, County Dublin, Ireland
June 25-30, 2013

Abstracts of the International Behavioral Neuroscience Society, Volume 22, June 2013

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IBNS CENTRAL OFFICE

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Greetings from the President.

Céad míle fáilte! A hundred thousand welcomes to our meeting in Ireland! As an Applachian hill-billy, I suspect that a few of my genes are Irish, and this is true of more than a few for my husband, whose genes seem to zero in on County Cork. We are meeting in the lovely sea-side town of Malahide, with Dublin and its cultural and entertainment attractions not far away, and at the beginning of summer. There is certain to be something for everyone to enjoy, at this venue

…..and also at the IBNS meeting. The Program Committee has organized a lovely set of talks, symposia, and posters. Judging from the list of those already registered, this is likely to be another very well attended meeting, following on the heels of our record-breaking meeting in Hawaii last year.

The core function of IBNS is to encourage research in behavioral neuroscience by fostering free and open communication and scientific exchange among its members and their academic institutions. Our meetings are the principal avenue by which this function is realized, and I am delighted to see each and every one of you here.

Caroline Blanchard
President, International Behavioral Neuroscience Society

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IBNS OUTSTANDING ACHIEVEMENT AWARD

The Fellows and Honorific Awards Committee is pleased to announce the *2014 IBNS Outstanding Achievement Award for Scientific Contributions to the field of Behavioral Neuroscience* is awarded to Robert J. Blanchard, Professor, University of Hawaii. Bob's research focuses on biobehavioral emotion systems, including aggression and defense, and the behavioral and physiological consequences of social stress. He has served on the Editorial Boards of *Neuroscience and Biobehavioral Reviews*, *Behavioral Processes*, *Journal of Comparative Psychology*, and *Pharmacology, Biochemistry & Behavior* and has published over 250 journal articles. Bob also served as President of the IBNS in 2003.

TRAVEL AWARDS

We are pleased to announce the recipients of the IBNS Travel Awards for the 2013 meeting in Ireland. 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.

TRAVEL AWARDS
(listed alphabetically)

Postdoctoral Travel Awards

Michal Arad, University of Maryland, Baltimore, Maryland, MD, USA
Lisa Briand, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
Stephen Mahler, Medical University of South Carolina, Charleston, SC, USA
Joanna L. Workman, University of British Columbia, Vancouver, Canada
Armin Zlomuzica, Ruhr-University of Bochum, Bochum, Germany

Graduate Student Travel Awards

Ryan Bastle, Arizona State University, Tempe, AZ, USA
Michael J. Corley, University of Hawaii at Manoa, Honolulu, HI, USA
Alexandre Hoeller, Federal University of Santa Catarina, Florianópolis, Brazil
Ann N. Hoffman, Arizona State University, Tempe, Arizona, AZ, USA
Linnet Ramos, University of Sydney, Sydney, Australia
Sergey Sotnikov, Max Planck Institute of Psychiatry, Munich, Germany
Farah Wahida Suhaimi, Universiti Sains Malaysia, Penang, Malaysia
Brandon Lee Warren, Florida State University, Tallahassee, FL, USA

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The IBNS would like to express our gratitude to the following organizations that have given financial support to the 22nd International Behavioral Neuroscience Society Conference.

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**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

Stephen Kent, Chair, La Trobe University, Melbourne, Australia
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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.ibnshomepage.org/?page=Committees.

PROGRAM

Tuesday, June 25

10:00-1:00 **Council Meeting** – *Marconi Room*

2:00-4:00 **Student & Post-Doc Only Social** – *Matt Ryan Bar.*

4:00-6:00 **Registration** – *Main Lobby*

7:00-9:00 **Welcome Reception** – *Guttenberg Suite*

Wednesday, June 26

8:30-10:30 **Symposium: Neurobiology and behavioral consequences of estradiol signaling in the brain.** Chair: **Robert Meisel**. *Tara Suite*

8:30 Estradiol feminizes the female brain during a specific prepubertal period. Bakker, J.

9:00 Estrogen receptor regulation of metabotropic glutamate receptor signaling in the female rat nucleus accumbens: Anatomical and behavioral changes underlying addiction. Mermelstein, P.

9:30 Membrane actions of estradiol in the regulation of female sexual behavior. Micevych, P.

10:00 Effects of Female Sexual Experience on Neuronal Plasticity. Meisel, R.L.

8:30-10:30 **Symposium: Circadian rhythm and sleep behavior in drosophila.** Chair: **Norio Ishida**. *Guttenberg Suite*

8:30 Genetics of sleep: Using a Drosophila model to identify molecular underpinnings. Sehgal, A.

9:00 Phosphorylation regulates multiple processes to keep circadian time. Hardin, P.

9:30 Molecular neurogenetics of biological rhythms in an intertidal crustacean. Kyriacou, C.; Zhang, L.; Wilcockson, D.; Hastings, Mi.; Webster, S.

10:00 Molecular and behavioral approach to understand circadian mating behavior in Drosophila. Ishida, N.; Suzuki,T.; Sakata, K.; Ito, K.; Hui, P.; Kawasaki, H.

10:30-11:00 **Coffee/Tea Break**. *Tara Suite*

11:00-12:00 **Keynote: John F. Cryan**, University College Cork, Ireland. **Mind-altering microbes: Role of gut microbiota on brain and behavior.** *Tara Suite*

12:00-1:30 **Break**
Council Meeting (continued**) –** Coast Restaurant

1:30-3:30 **Symposium: Nicotine reinforcement and dependence: Neuroadaptations in stop and go signals.** Chair: **Nicholas W. Gilpin.** *Guttenberg Suite*

1:30 The role of the interpeduncular nucleus in nicotine withdrawal. Tapper, A.

2:00 Habenular signaling in nicotine reinforcement. Tuesta, L.; Fowler, C.; Lu, Q.; Kenny, P.

2:30 Identification of CRF neurons in the VTA that control the aversive effects of nicotine withdrawal. George, O.

3:00 Nicotine Vapor Inhalation Escalates Nicotine Self-Administration. Gilpin, N.W.

1:30-3:30 **Symposium**: **Social aggression.** Chair: **Newton Sabino Canteras**. *Tara Suite*

1:30 Is short term potentiation the physiological basis of aggression escalation? Potegal, M.

2:00 Ventral premammillary nucleus as a critical sensory relay to the maternal aggression network. Canteras, N.

2:30 Hunting for an aggression locus in mice. Lin, D.

3:00 Adolescent social stress in rats: Adult behavioral and neurobiological consequences. Buwalda, B.; Coppens, C.M.; van Drunen J.; Koolhaas, J.M.

3:30-4:00 **Coffee/Tea Break**. *Tara Suite*

4:00-6:00 **Symposium: The endocrine disrupting compounds: What they are, where they are and how they change behavior.** Chair: **Cheryl S. Rosenfeld**. *Guttenberg Suite*

4:00 Effects of endocrine disruptors on sexually selected behavioral traits. Rosenfeld, C.S.

4:30 Prenatal bisphenol A impairs social memory and alters juvenile social behavior over multiple generations. Wolstenholme, J.T.; Rissman, E.F.

5:00 Environmentally relevant concentrations of endocrine disrupting compounds can disrupt amphibian mating behavior. Hoffmann, F.; Kloas, W.

5:30 Effects of an endocrine disruptor on anxiety behaviour in fish - Examples from zebrafish and guppy. Hallgren, S.

4:00-6:00 **Symposium: Stop mechanisms in normal behavior and in obsessive compulsive disorder.** Chairs: **Kurt Hoffman; Henry Szechtman.** *Tara Suite*

4:00 The end to uncertainty – Yedasentience in normal and abnormal behavior. Szechtman, H.; Woody, E.Z.

4:30 Starting and ending phases in motor behavior: The delimiters of pragmatism and stereotypy. Eilam, D.; Keren, H.; Mort, J.

5:00 What can studies of behavioural control in rats tell us about human stopping? Eagle, D.

5:30 The rabbit as a model system for studying stopping mechanisms involved in normal, adaptive behavior. Hoffman, K.L.; Morales, R.R.

6:00-8:00 **Break**

8:00-10:00 **Poster Session 1: Animal models of behavioral disorders.** *Guttenberg Suite*

1. Behavioral Correlates of Risky Decision-Making and Executive Functions. Shimp, K.G.; Beas, B.S.; Mitchell, M.R.; Bizon, J.L.; Setlow, B.

2. Administration of nimodipine during the sensitive period for brain sexual-differentiation leads to sex-specific behavioral effects in adulthood: Neurodevelopmental implications for depression. Arad, M.[Travel Award]; McCarthy, M.M.; Gould, T.D.

3. Chronic corticosterone treatment enhances operant extinction-induced despair and impairs HPA-axis activity as a function of age. Komorowski, M.; Topic, B.; Lamounier-Zepter, V.; Huston, P.

4. Sex has limited influence on manic-like behavior of Black Swiss mice. Ene, H.; Kara, N.Z.; Einat, H.

5. Increased monoamine transporter activity plays an important role in pro-inflammatory cytokine-induced anhedonia. van Heesch, F.; Prins, J.; Korte-Bouws, G.A.H.; Westphal, K.G.C.; Olivier, B.; Kraneveld, A.D.; Korte, S.M.

6. GABAergic signaling alterations contribute to impaired working memory in aged F344 rats. Bañuelos, C.; Beas, B.S.; McQuail, J.A.; Gilbert, R.J.; Setlow, B.; Bizon, J.L.

7. Not presented.

8. White matter fractional anisotropy and social impairments in children and adolescents with autism. Noriuchi, M.; Kikuchi, Y.; Kamio, Y.

9. The influence of age on the visual side-bias of pigeons (Columba livia). Kelly, D.M.

10. Maternal separation-induced hypoactivity in the open field is reversed by exercise in male but not female rats: Effects accompanied by changes in orexin function. James, M.H.; Campbell, E.J; Richardson, H.N.; Hodgson, D.M.; Dayas, C.V.

11. Interactive effect of serotonin deficiency, early life stress and maternal presence on corticosterone response to a psychosocial stressor. Priddy, W.; Herod, S.M.

12. Epigenetic bidirectional rescue of extreme genetic predispositions to anxiety: Impact of CRH receptor 1 in the amygdala. Sotnikov, S.V.[Travel Award]; Markt, P.O.; Avrabos, C.; Malic, V.; Chekmareva, N.U.; Naik, R.; Sah, A.; Singewald, N.; Schmidt, M.; Eder, M.; Landgraf, R.

13. The genetic model of seizure states. Fedotova, I.B.; Surina, N.M.; Poletaeva, I.I.

14. Cataleptic states of different origin, observing in Krushinsky-Molodkina (KM) rats, selected for audiogenic epilepsy proneness. Surina, N.

15. Vicarious social defeat induces depression- and anxiety-like behavior in adolescent mice and increases nicotine consumption. Warren, B. [Travel Award]; Alcantara, L.; Vialou, V.; Parise, E.; Iñiguez S.; Nestler, E.; Bolaños-Guzmán, C.

16. Exaggerated behavioural and HPA axis responses to stress in the non-obese diabetic (NOD) mouse. McGuinness, B.; Gibney, S.M.; Harkin, A.; Connor, T.J.

17. Stressor-induced IL-6 production and signalling: Divergence in responses between the periphery and CNS. McGuinness, B.; Gibney, S.M.; Harkin, A.; Connor, T.J.

18. Not presented.

19. Simulated shift work and development of type 2 diabetes in mice. Toth, L.A.; Trammell, R.A.

20. c-Fos Up-Regulation Differences between the C57BL/6 N and J Mice Substrain in the mPFC Brain Region that is Related to Emotional Perseveration. Landrau-Giovannetti, S.; Sáez, E.; Peña de Ortiz, S.; Méndez-Merced, A.

21. Neurodevelopmental effects of early life stress, serotonin deficiency and maternal presence on adulthood psychosocial behaviors. Lewandowski, K.; Herod, S.M.

22. Effects of repeated fluoxetine and paroxetine exposure on anxiety-like behaviors. Crawford, C.A.; Humphrey, D.E.; Powers, C.; Valentine, J.M.

23. Chronic stress impacts nonassociative fear and alters amygdala-hippocampal functional network activation. Hoffman, A.N. [Travel Award]; Lorson, N.G.; Hanna, J.J.; Mazur, G.J.; Taylor, S.B.; Yahn, S.L.; Sanabria, F.; Olive, M.F.; Conrad, C.D.

24. Relaxin-3/RXFP3 neural networks and control of arousal- and stress-related behaviours. Gundlach, A.L.; Ma, S.; Blasiak, A.; Smith, C.M.; Ganella, D.E.; Ryan, P.J.; Hosken I.T.; Lawrence, A.J.; Bathgate, R.A.D.; Olucha-Bordonau, F.E.

25. Neurobiological effects of contingency training in male rats exhibiting predisposed coping strategies: Implications for depression. Lambert, K.G.; Hyer, M.M.; Hazelgrove, A.; Rzucidlo, A.; Bergeron, T.; Bardi, M.

26. Not presented.

27. Interaction of a dietary supplement with lithium in a rat model of mania. McMillen, B.A.; Nagchowdhuri, P.S.; Carr, C.E.; Cormier, Z.A.; Williams, H.L.

28. Not presented.

29. Pro-social ultrasonic communication in rats: Social-communication deficits after post-weaning but not post-adolescence social isolation - phenotypic rescue by re-socialization. Seffer, D.; Rippberger, H.; Schwarting, R.K.W.; Wöhr, M.

30. Antidepressant-like effects following single or repetitive NOS inhibitors administration in mice: Comparison with fluoxetine. Oliveira, R.M.W.; Leal, V.M.S.; Bonassoli, V.T.; Milani, H.; Del Bel, E.

31. Chronic unpredictable mild stress alters an anxiety-related defensive response, Fos immunoreactivity and hippocampal adult neurogenesis. de Andrade, J.S.; Abrão, R.O.;

Céspedes, I.C.; dos Santos, T.B.; Diniz, L.; Britto, L.R.G.; Spadari-Bratfisch, R.C.; Ortolani, D.; Melo-Thomas, L.; da Silva, R.C.B.; Viana, M.B.

32. Evidence for behavioral sensitization to stress in rats using variations of the noise test. Heyser, C.J.; Rosen, M; Yochum, C.L.

33. Oldie but Goldie? Advanced paternal age increases the offspring's risk of developing neuropsychiatric phenotypes. Rippberger, H.; Seffer, D.; Kircher, T.; Krug, A.; Schwarting, R.K.W.; Wöhr, M.

34. Changes in cortical-brainstem functional connectivity during repeated social stress in mice. Franklin, T.B.; Vyssotski, A.; Gross, C.

35. Different temporal courses of motor and cognitive deficits in a progressive animal model of Parkinson's disease. Santos, J.R.; Dierschnabel, A.L.; Campêlo, C.L.C.; Leão, A.H.F.F.; Macedo, P.T.; Silva, A.F.; Engelberth, R.C.G.J.; Cavalcante, J.S.; Abílio, V.C.; Izídio, G.S.; Silva, R.H.; Ribeiro, A.M.

36. Doxycycline restrains glia and confers neuroprotection in a 6-OHDA Parkinson model. Lazzarinia, M.; Martin, S.; Mitkovski, M.; Vozarie, R.R.; Stühmer, W.; Del Bela, E.

37. Behavioral Characterization of Sindbis Virus Infected Mice. Potter, MC.; Baxter, VK.; Wozniak, K.M.; Griffin, D.E.; Slusher, B.S.

38. Different learning and memory performance in an APP/PS1 mouse model of Alzheimer's disease with chronically reduced BDNF. Psotta, L.; Rockahr, C.; Veit, M.; Kirches, E.; Bock, J.; Braun, A. K.; Lessmann, V.; Endres, T.

39. Anxiolytic-like effects exerted by serotonin at 5-ht2c receptors may be modulated by 5-ht3 receptors located within the mouse periaqueductal gray matter. Canto-de-Souza, A.; Lopes, L.T.; Nunes-de-Souza, R.L.

40. Effects of chronic exposure to predator-associated stimuli on HPA-axis activation and anxiety-like behavior in mice. Birkett, M.; Redding, C.; Greene, T.

41. Behavioral profile and hippocampal neurogenesis in an animal model of generalized anxiety disorder. Dias, G.P.; Bevilaqua, M.C.N.; Silveira, A.C.D.L.; Fleming, R.L.; Carvalho, L.A.; Cocks, G.; Beckman, D.; Hosken, L.C.; Machado, W.S.; Corrêa-e-Castro, A.C.; Mousovich-Neto, F.; Gomes, V.C.; Bastos, G.N.T.; Kubrusly, R.C.C.; Corrêa da Costa, VM.; Srivastava, D.P.; Landeira-Fernandez, J.; Nardi, A.E.; Thuret, S.; Gardino, P.F.

42. Reduced hippocampal volume in the Wistar-Kyoto rat as determined by high resolution anatomical MRI is associated with depressive and anxiety related behaviours. Gormley S.; Kerskens, C.; Harkin, A.

43. Effects of genetic background on visceral nociception, anxiety and depression-like behaviour: Responses of 12 mouse strains. Moloney, R.D.; Dinan, T.G.; Cryan, J.F.

44. Chronic minocycline attenuates depressive-like behaviour and peripheral nerve injury-induced mechanical and cold allodynia in the olfactory bulbectomised rat. Burke, N.N.; Chen, S.; Finn, D.P.; Roche, M.

45. Social behavioural deficits in a rat model of autism are associated with enhanced hippocampal N-acylethanolamine levels. Kerr, D.M.; Downey, L.; Conboy, M.; Finn, D.P.; Roche, M.

46. Involvement of different subnuclei of the dorsal raphe nucleus in the panicolytic-like effect caused by prelimbic cortex activation in rats. Zangrossi, H.; Spiacci, A.; Yamashita, P.S.M.

47. Ghrelin regulates anxiety-like behavior in mice potentially through hypothalamic-purity-adrenal axis interaction. van Oeffelen, W.E.P.A.; Clarijs, A.W.H.C.; Dinan, T.G.; Cryan, J.F.

48. Not presented.

49. Comparison of two different protocols of chronic social defeat in adolescent C57BL/6 male mice on anxiety and depression-related behaviors. Chiavegatto, S.; Amaral, C.E.; Soares, R.B.; Rodrigues, A.C.D.; Reigado, C.N.; Resende, L.S.; Alves-dos-Santos, L.

50. Adverse social environment in early life that has selective long-lasting effects on social interaction and plasma oxytocin of adult rats. Henriques, T.P.; Diehl, L.A.; Corrêa, C.N.; Pardo, G.E.; Souza, M.A.; Caceres, R.C.; Winter, A.; de Almeida, R.M.M.; Dalmaz, C.; Lucion, A.B.

51. Contextual Fear Conditioning in Maternal Separated Rats: The Amygdala as a site for alterations. Diehl, L.A.; Laureano, D.P.; Benitz, A.N.D.; Noschang, C.; Ferreira, A.G.K.; Scherer, E.B.; Machado, F.R.; Henriques, T.P.; Wyse, A.T.S.; Molina, V.; Dalmaz, C.

52. Increased social anxiety and alteration of serotonergic gene expression after priming of CRF receptors in the bed nucleus of the stria terminalis. Donner, N.C.; Mani, S.; Johnson, P.L.; Fitz, S.D.; Shekhar, A.; Lowry, C.A.

53. Not Presented.

54. Not presented.

55. Not presented.

56. Schizophrenia-like abnormalities in mice due to adolescent exposure to Toxoplasma gondii. Kannan, G.; Li, Y.; Xiao, J.C.; Severance, E.G.; Jones-Brando, L.; Yolken, R.H.; Pletnikov, M.V.

57. The microbiome-gut-brain axis regulates the survival of newly-born cells in the adult hippocampus. Ogbonnaya, S.; Cryan, J. F.; O'Leary, O.F.

Thursday, June 27

8:30-10:30 **Symposium: Animal models of autism: Assessing genetic vulnerability, environmental risk factors, and new strategies for intervention.** Chair: **Tomasz Schneider.** *Guttenberg Suite*

8:30 Mouse models of autism phenotypes as preclinical screens for drug discovery. Moy, S.S.; Teng, B.L.; Nonneman, R.J.; Agster, K.L.; Nikolova, V.D.; Davis, T.T.; Riddick, N.V.; Baker, L.K.; Pedersen, C.A.; Jarstfer, M.B.

9:00 Animal model of autism induced by prenatal exposure to valproic acid. Schneider, T.

9:30 Autism spectrum disorders, epigenetics and histone deacetylase inhibitors. Regan, C.

10:00 Autism spectrum disorders and the primate brain. Watson, K.; Platt, M.

8:30-10:30 **Symposium**: **Female vulnerability to depression: From molecules to behavior.** Chairs: **Debra Bangasser; Christina Dalla.** *Tara Suite*

8:30 Animal models of depression: How about females? Dalla, C.

9:00 Sex differences in stress-related psychiatric disease: Novel mechanisms for interactions between stress and arousal systems. Bangasser, D.A.; Ding, H.; Seeholzer, S.; Valentino, R.J.

9:30 Epigenetic regulation of sex differences in the behavioral response to stress. Hodes, G.E.; Pfau, M.; Ahn, H.F.; Liu, X.; Christoffel, D.J.; Golden, S. A.; Heshmati, M.; Feng, J.; Shen, L.; Nestler, E.J.; Russo, S.J.

10:00 Structural Plasticity and Cognitive Function: Resilience and Vulnerability During the Postpartum Period. Leuner, B.

10:30-11:00 **Coffee/Tea Break**. *Tara Suite*

11:00-12:00 **Bench-to-Bedside Lecture: Phil Skolnick, Ph.D., D.Sc. (hon.)**, National Institute on Drug Abuse. **Developing drugs to treat substance use disorders (SUDS): Why haven't we been more successful?** *Tara Suite*

12:00-1:30 **Break**

12:00-1:30 **Workshop: What's your digital reputation and why you should care! *How and what does it say about you way before that first call or email?* Sam Stanton**, Redbutton.tv

Sam Stanton is the CEO at redbutton.tv, the leader in social media and relevant technology for events. Simply put, they help people connect with their audiences. Sam will share ***WHY*** you should engage social media and takes the "scary, sometimes complicated" tech and social world and makes it fun while helping you understand how to easily harness its power! You're guaranteed to laugh, have some fun, and most importantly leave the workshop with a new understanding of social media and how/why you need to manage your digital reputation!

1:30-3:30 **Oral Session 1: TBI, psychosis, and depression.** Chair: **Stephen Kent.** *Tara Suite*

1:30 Administration of nimodipine during the sensitive period for brain sexual-differentiation leads to sex-specific behavioral effects in adulthood: Neurodevelopmental implications for depression. Arad, M.[Travel Award]; McCarthy, M.M.; Gould, T.D.

1:42 Transcranial infrared laser stimulation of human cognitive and emotional functions. Gonzalez-Lima, F.; Barrett, D.W.

1:54 Reduced sociability is exhibited by alterations in scent marking and ultrasonic vocalizations after traumatic brain injury (TBI) in the developing mouse. Semple, B.D.; Adahman, Z.; Hollingsworth, C.; Gimlin, K.; Noble-Haeusslein, L.; Schenk, A.K.

2:06 Sodium selenate treatment reduces hyperphosphorylated tau and improves behavioral outcome in an animal model of repeated brain concussion. Shultz, S.; Tan, X.L.; Wright, D.; O'Brien, T.

2:18 Social cognition in a 'two hit' model of psychosis: Male-specific additive effects of methamphetamine treatment and genetic depletion of brain-derived neurotrophic factor. Manning, E.E.; van den Buuse, M.

2:30 Neuropeptide Mechanisms and Treatment Targets in Stress-Induced Psychiatric Disorders. Ronan, P.J.

2:42 Tail suspension test: Study of behavioral structure in male and female swiss mice. Ramos Costa, A.P.; da Silva Santos, E.C.; Lino-de-Oliveira, C.; Monteiro De Lima, T.C.

2:54 microRNAs as Novel Antidepressant Targets in Refractory Depression: Converging Effects of Ketamine and Electroconvulsive Shock Therapy. O'Connor, R.M.; Dinan, T.G.; Cryan, J.F.

3:06 Investigating neuroendocrine changes and the impact of pre-treatment of Antalarmin on depressive-like behaviour in a rat model of global cerebral ischemia. de la Tremblaye, P.B.; Raymond, J.; Plamondon, H.

3:18 Trehalose induced antidepressant-like effects and autophagy enhancement in mice. Einat, H.

1:30-3:30 **Oral Session 2: HIV and addiction**. Chair: **Mikhail Pletnikov**. *Guttenberg Suite*

1:30 The role of αCaMKII autophosphorylation in the establishment of alcohol drinking behaviour in mice. Müller, C.P.

1:42 Environmental perturbation, inflammation and behavioral fatigue in healthy and virus-infected mice. Toth, L.A.; Trammell, R.A.

1:54 Temporal processing demands implicate perceptual and gating deficits in the HIV-1 transgenic rat. Booze, R.M.; Moran, L.M.; Mactutus, C.F.

2:06 Characterization of core components of executive function in HIV-1 Transgenic Rats. Mactutus, C.F.; Moran, L.M.; Booze, R.M.

2:18 The gut metabolite, S-equol, as a therapeutic for attentional deficits in HIV-1 transgenic rats. Moran, L.M.; Booze, R.M.; Mactutus, C.F.

2:30 ApoE genotype affects brain activity during nicotine use and withdrawal. Rose, G.M.; Coppens, R.; Diggs, H.; Kanneganti, R.; Gilbert, D.G.

2:42 Nicotine enhances the sign-tracking but not the goal-tracking response to a food-associated cue. Meyer, P.J.

2:54 Gut peptide GLP-1 and its analogue, Exendin-4, decrease alcohol intake and reward. Shirazi, R.H; Dickson, S.L.

3:06 Heavy episodic beer drinking enhances glutamate uptake in the prefrontal cortex of adolescent relative to adult C57BL/6J mice. Morales, K.; Lugo, N.; Melendez, R.I.

3:30-4:00 **Coffee/Tea Break.** *Tara Suite*

4:00-6:00 **Symposium:** New **horizons in nutrition, brain function and behavior.** Chair: **Robin B. Kanarek**. *Guttenberg Suite*

4:00 Modeling the metabolic modulation of behavior – the case of b-vitamins and dementia. Troen, A.M.

4:30 Omega-3 polyunsaturated fatty acids and depression. Giles, G.

5:00 Creatine's role in brain function and affective behavior. D'Anci, K.E.

5:30 Acute and longer term effects of breakfast consumption on behavior. Smith, A.P.

4:00-6:00 **Symposium: Broken clocks, inflammatory overload, and social pressures: Modeling stressors of the modern world and their effects on brain and behavior.** Chair: **Ilia Karatsoreos**. *Tara Suite*

4:00 Good stress, bad stress, and the effects on neural and behavioral function. McEwen, B.

4:30 Clocks interrupted: Effects of sleep and circadian disruption on neural plasticity and behavior. Karatsoreos, I.

5:00 Chronic psychosocial stress effects on emotions, inflammatory state and adrenal functions: Reversal by oxytocin? Neumann, I.D.; Peters, S.; Reber, S.O.

5:30 Neuroimmune mechanisms underlying stress-induced immunosuppression. Harkin, A.; Curtin, N.M.; Mills, K.H.G.; Boyle, N.T.; Connor, T.J.

6:00-8:00 **Break**

8:00-10:00 **Poster Session 2: Behavioral pharmacology and addiction models.**
Guttenberg Suite

58. Exposure to oxytocin during adolescence produces long-term impairments in sociosexual behaviors in male rats. Harding, S.M.; Andreychik, M.R.

59. Decision making in methamphetamine-treated rat. Mizoguchi, H.; Fukumoto, K.; Wang, T.; Sato, J.; Yamada, K.

60. Effects of maternal stress and perinatal fluoxetine exposure on behavioural outcomes of adult offspring. Kiryanova, V.; Iablokova, S.; Dyck, R.H.

61. Changes in endocannabinoid system may be involved with depressive-like behavior in streptozotocin-induced diabetic rats. de Morais, H.; Pasquini, C.S.; da Silva, L.M.; Maria-Ferreira, D.; Cunha, J.M.; Zanoveli, J.M.

62. Developmental fluoxetine exposure affects hippocampal neurogenesis in adult rat offspring. Rayen, I.; Steinbusch, H.W.M.; Pawluski, J.L.

63. Neurogenesis is not required for lithium's mood stabilizing-like effects. Kara, N.Z.; Agam, G.; Einat, H.

64. Effects of early life environmental enrichment on behavioural responses and BDNF levels of an animal model of schizophrenia – the SHR strain. Santos, C.M.; Peres, F.F.; Gouvea, D.G.; Vendramini, A.M.; Levin, R.; Calzavara, M.B.; Abílio,V.C.

65. Effects of cannabinoid drugs on prepulse inhibition of startle in an animal model of schizophrenia: The SHR (Spontaneously Hypertensive Rats) strain. Levin, R.; Peres, F.F.; Almeida, V.; Calzavara, M.B.; Zuardi, A.W.; Hallak, J.E.; Crippa, J.A.; Abílio, V.C.

66. The 5-HT1A/1B receptor agonist eltoprazine has anti-impulsive properties and alters brain monoamine levels without enhancing brain stimulation reward. Prins, J.; Van den Bergh, F.S.; Dupree, R.; Korte-Bouws, G.A.H.; Westphal, K.G.C.; Oosting, R.S.; Olivier, B.; Korte, S.M.

67. Acute prosocial effects of peripherally administered oxytocin, MDMA and their combination in rats: A possible common mechanism of action involving the V1A receptor. Ramos, L. [Travel Award]; Hicks, C.; Kevin, R.; Caminer, A.; McGregor, I.S.

68. Cannabidiol effects in the prelimbic cortex depend on 5-HT1A receptors and previous stress experience. Fogaça, M.V.; Campos, A.C.; Fernando, M.C.V.; Reis,; Guimaraes, F.S.

69. Knockdown of glutamate receptor interacting protein (GRIP) within the nucleus accumbens enhances reinstatement of cocaine seeking and alters synaptic plasticity. Briand, L.A. [Travel Award]; Kimmey, B.; Ortinski, P.I.; Huganir, R.L.; Pierce, R.C.

70. Inhibition of Ventral Pallidum Projection to VTA Blocks Cue-Triggered Cocaine Seeking. Mahler, S.V. [Travel Award]; Vazey, E.M.; Kaufling, J.; Roth, B.L.; Aston-Jones, G.

71. Effects of cannabinoid and vanilloid drugs on positive and negative-like symptoms in an animal model of schizophrenia – the SHR strain. Almeida, V; Peres, F.F.; Levin, R.; Suiama, M.; Abílio, V.C.

72. Overactivation of muscarinic cholinergic receptors leads to long-term anxiogenic responses associated with hippocampal theta rhythm activity and HPA axis alterations. Hoeller, A.A.[Travel Award]; Spiga, F.; Lightman, S.L.; Collingridge, G.L.; Bortolotto, Z.A.; De Lima, T.C.M.

73. Effect of decabrominated diphenyl ether (BDE-209) exposure during breast milking on the learning and memory function in the CD-1 mice. Tseng, L.H.; Ho, Y.J.; Hsu, P.C.; Chang, S.H.

74. Sex differences in impulsive action: Dissociation between systemic and intra-mPFC glutamate antagonism and the effect of amphetamine exposure. Hammerslag, L.; Waldman, A.; Arogundade, A.O.; Weaver, J.; Gulley, J.

75. Evidence for altered 5-HT2C receptor function in rats exposed to amphetamine during adolescence or adulthood. Hankosky, E.; Kofsky, N.; Gulley, J.

76. The role of glycine transmission in the medial preoptic area in regulation of male rats sexual behavior. Zhuravleva, Z.D.

77. Sex differences in pharmacokinetic of acute administration of methamphetamine in adult Wistar rats. Šlamberová, R.; Bubeníková-Valešová, V.; Syslová, K.; Rambousek, L.; Kačer, P.

78. Facilitation of 2-arachidonoylglycerol (2ag) signaling in the dorsolateral periaqueductal gray in rats induced anxiolytic-like effects. Gobira, P.H.; Almeida-Santos, A.F.; Moreira, F.A.; Aguiar, D.C.

79. The facilitating effects of testosterone-sildenafil co-treatment on sexual behavior in female rats depend on the delayed effects of testosterone. Bijlsma, E.Y.; Jonker, M.; Bloemers, J.; Tuiten, A.; Olivier, B.; Oosting, R.

80. Amphetamine exposure during adolescence alters dopaminergic modulation of inhibitory transmission in the medial prefrontal cortex. Kang, S.; Paul, K.; Cox, C.L.; Gulley, J.M.

81. Sex differences in central amygdala GABAergic neuron density and anti-anxiety efficacy of diazepam in outbred lines of high and low anxiety Long Evans rats. Donaldson, S.T.; Ravenelle, R.; Niedzielak, T.

82. Ethanol induced motor impairment involves inhibition of α7 nAChRs. Wolfman, S.L.; McDaid, J.; Gallagher, K.; McGehee, D.S.

83. Participation of the Serotonin and Angiotensin-(1-7) in behavioral responses in transgenic rats with low brain angiotensinogen. Almeida-Santos, A.F.; Kangussu, L.M.; Campagnole-Santos, M.J.; Aguiar, D.C.

84. Regulation of arc through miR-495 as a potential mediator of cocaine motivation and extinction learning. Bastle, R. [Travel Award]; Pentkowski, N.; Turk, M.; Adams, M.; Berger, A.; Dado, N.; Smith, K.; Hammer, R.; Perrone-Bizzozero, N.; Neisewander, J.

85. Repeated administration of cannabidiol induces an anxiolytic-like effect in mice submitted to chronic unpredictable stress by facilitation of endocannabinoid neurotransmission. Fogaça, M.V.; Guimarães, F.S.

86. Effects of fluoxetine in corticosterone-induced depressive-like phenotypes in postpartum and nulliparous females. Workman, J. [Travel Award]; Kitay, M.F.; Chow, C.; Galea, L.A.M.

87. The effects of calorie restriction on fever and neuroimmune communication pathways in mice. Radler, M.; Smith, G.; Hale, M.W.; Kent, S.

88. Fos expression after exposure to social and nicotine rewards or reward-conditioned environments in adolescent male rats. Peartree, N.A.; Williams, A.M.; Bastle, R.M.; Goenaga, J.; Chandler, K.N.; Hood, L.E.; Neisewander, J.L.

89. Effects of harmane on prepulse inhibition in rats. Kayir, H.; Kilicarslan, I.; Kara, A.; Calik, M.; Goktalay, G.; Uzbay, T.

90. Not presented.

91. Participation of NK1 receptors of the amygdala on the processing of different types of fear. Carvalho, M.C.; Santos, J.M.; Brandão, M.L.; Ribeirão Preto, S.P.

92. Effects of fluoxetine exposure during adolescence on cocaine CPP in adulthood. Nieto, S.; Riggs, L.; Dayrit, G.; Cao, V.; Zamora, N.; Rodriguez, R.; Warren, B.; Iñiguez, S.

93. Relapse to methamphetamine-seeking behaviour is reduced by oxytocin administration in the nucleus accumbens core of the rat. Baracz, S.J.; Everett, N.A.; McGregor, I.S.; Cornish, J.L.

94. Lateral habenula lesions reduce the anxiogenic response to self-administered cocaine. Shelton, K.; Wenzel, J.; Sved, S.; Ettenberg, A.;

95. The anabolic steroid, 17α-methyltestosterone, accelerates the transition from rough and tumble play towards sexual-related behaviors. Silva-Gotay, A.; Ramos-Pratts, K.; Barreto-Estrada, J.L.

96. The potential role of neurexins and neuroligins in the pharmacological and behavioral effects of nicotine. Bernardi, R.E.; Uhrig, S.; Spanagel, R.; Hansson, A.C.

97. Effects of anxiolytic and anxiogenic drugs on defensive behaviour of mice exposed to an elevated plus-maze. Nunes-de-Souza, R.L.; Sorregotti, T.; Mendes-Gomes, J.; Rico, J.L.; Rodgers, R.J.

98. Serotonin-induced postprandial behavior sequence in pigeons (Columba livia): Participation of 5-HT1A receptor. Dos Santos, T.S.; Melleu, F.F.; Krueger, J.; Azevedo, F.; Poli, A.; Marino-Neto, J.

99. Microbiota is Essential for Social Development in the Mouse. Desbonnet, L.; Clarke, G.; Shanahan, F.; Dinan, T.G.; Cryan, J.F.

100. Decreased dopaminergic neurotransmission produces inverse incentive learning in rats: A role for D1-like receptors. Beninger, R.J.; Xu, K.; Banasikowski, T.J.

101. Quantification by LC-MS/MS of psychotropic drugs in different mice tissues. Manadas, B.; Pinto, J.; Mendes, V.M.; Ferreira, A.I.S.; Rocha, S.; Costa Pereira, J.; Baltazar, G.; Cotter, D.; Dunn, M.

102. Ventral midbrain neurotensin sensitizes to amphetamine-induced locomotor activity through activation of extracellular signal-regulated kinases. Rompré, P.-P.; Voyer, D.; Lévesque, D.

103. Not presented.

104. Angiotensin (5-8) induces anxiogenic-like effects in the ventrolateral periaqueductal gray through angiotensin type 1 receptor activation. Borelli, K.G.; Juliano, M.A.; Prado, W.A.; Brandão, M.L.; Martins, A.R.

105. Chronic interferon alpha administration induces thermal hyperalgesia in mice. Fitzgibbon, M.; Burke, N.N.; Finn, D.P.; Roche, M.

106. Not presented.

107. Not presented.

108. Cross-tolerance between nicotine and ethanol is accompanied by increased ethanol self-administration. McDaid, J.; Metz, R.A.E.; Kamber, R.; Wolfman, S.L.; McGehee, D.S.

109. Functional consequences of methylphenidate exposure during postnatal days 11-20 on oxycodone reward in male and female adolescent rats. Zavala, A.R.; Esqueda, M.A.; Ojala, K.S.; Langa, R.M.

110. CB1 receptors in the RVM mediate the antinociceptive effects of the FAAH inhibitor URB597 in Wistar-Kyoto rats. Rea, K.; Olango, W.; Okine, B.; Coyle, K.; Harhen, B.; Roche, M.; Finn, D.

111. Behavioral characterization of the hallucinogen 2,5-dimethoxy-4-iodophenethylamine (2C-I) and superpotent N-benzyl derivatives. Halberstadt, A.L.; Geyer, M.A.

112. Nocifensive behavior and neuroendocrine response after nociceptive stimulation in TRPV1 and TRPV4 knockout mice. Ueta, Y.; Ishikura, T.; Matsuura, T.; Yoshimura, M.; Ohkubo, J-I.; Maruyama, T.; Ohnishi, H.

Friday, June 28

8:30-10:30 **Symposium: Sex matters: Developmental influences have sex-dependent long-term consequences for behavior.** Chair: **Susanne Brummelte.** *Guttenberg Suite*

8:30 Contributions of hormones and genes to the sexual differentiation of song and partner preferences. Tomaszycki, M.

8:54 Early programming of stress-related alterations: Sex differences, molecular mechanisms and pharmacological implications for depression and addiction. Morley-Fletcher, S.

9:18 Sex-specificity in transgenerational epigenetic programming. Bale, T.

9:42 Sex matters: Developmental perturbations result in sex-dependent long-term consequences on neuroplasticity, behavior and HPA function. Galea, L.; Brummelte, S.

10:06 Fetal programming: Sex-specific and transgenerational consequences. Matthews, S.G.

8:30-10:30 **Symposium: Lost in translation: Improving the predictive validity of animal models for CNS disorders.** Chair**: David McKinzie.** *Tara Suite*

8:30 Leveraging 60 years of monoamine antipsychotic experience: Reducing clinical phase II failures for new schizophrenia medications. McKinzie, D.

9:00 Getting Smarter about Developing Drugs to Treat Cognitive Deficits in CNS Disorders: The use of Touchscreens in Drug Discovery. Dix, A.

9:30 Moving beyond current behavioral antidepressant animal models: Back translation of recent clinical findings to the bench. Witkin, J.M.

10:00 Mining and modeling human genetics in the search for autism therapeutics. Smith, D.

10:30-11:00 **Coffee/Tea Break**. *Tara Suite*

11:00-12:00 **Presidential Lecture: D. Caroline Blanchard, Ph.D.,** University of Hawaii, Honolulu, HI, USA. **The joy of a good model: Autism, heparan sulfate, and the BTBR mouse.** *Tara Suite*

12:00-1:30 **Break. Meet The Professionals Lunches.**

1:30-3:30 **Symposium: Molecular and cellular endophenotypes in neuropsychiatric disease: Homer proteins.** Chairs**: Karen K. Szumlinski; Tod E. Kippin.** *Guttenberg Suite*

1:30 Dopamine-glutamate interaction, antipsychotics and Homer. de Bartolomeis, A.

2:00 Homer as a regulator of pain sensitivity and heroin-induced rewarding effect. Obara, I.; Szumlinski, K.K..

2:30 Homer2: A molecular trigger for alcoholism? Szumlinski, K.K.

3:00 Role of Homer2 in regulation of adult neurogenesis: Implications for corticolimbic striatal function. Kippin, T.E.

1:30-3:30 **Symposium: Revisiting the role of medial septal neurons in learning and memory.** Chair: **Kevin Pang.** *Tara Suite*

1:30 Role of GABAergic medial septal neurons in working memory. Pang, K.

2:00 Septohippocampal GABAergic neurons and consolidation of memories. Cassel, J.C.; Koenig, J.; Lecourtier, L.

2:30 Cholinergic and noncholinergic functions of the hippocampus in episodic memory. Easton, A.

3:00 Alterations in cholinergic and noncholinergic basal forebrain neurons in aging: Consequences for cognition. Bizon, J.

3:30-4:00 **Coffee/Tea Break**. *Tara Suite*

4:00-6:00 **Symposium: Contribution of early environmental and genetic susceptibility to behaviour related to adult psychopathology.** Chairs: **Mikhail Pletnikov; John Waddington**. *Tara Suite*

4:00 Searching for early determinants of emotional reactivity and neuroendocrine responses to stress in animal models: From mice to non human primates. Cirulli, F.

4:30 Brain dysfunction induced by chronic stress in early life: Involvement of the stress-sensitive transcription factor NPAS4. Yamada, K.

5:00 Gene-environment interplay across the lifespan: Investigating etiopathological processes in schizophrenia using mutant models of gene disruption. O'Tuathaigh, C.

5:30 Interaction of mutant DISC1 with environmental adversities: Shared and unique mechanisms. Pletnikov, M.

4:00-6:00 **Symposium: A translational perspective on the neural circuitry of learning and decision making via positive and negative feedback.** Chairs: **Jonathan Brigman, Jared W. Young.** *Guttenberg Suite*

4:00 Dopaminergic influence on learning via positive and negative feedback. Young, J.W.; van Enkhuizen, J.; Higa, K.; Zhou, X.; Powell, S.B., Geyer, M.A.

4:30 The representation of time, probability and uncertainty by mice. Gallistel, C.

5:00 Prefrontal regulation of decision-making in a rat analogue of the Iowa Gambling Task. van den Bos, R.; Koot, S.; de Visser, L.

5:30 Updating expectation: Orbitfrontal cortex and flexible behavior. Sigdel, R.; Phillips, C.A.; Brigman, J.L.

6:00-8:00 **Break**

8:00-10:00 **Poster Session 3: Behavioral biology and development.** *Guttenberg Suite*

113. The role of cingulate cortex regions in subjective time perception. Kozlovskiy, S.; Pyasik, M.; Vartanov, A.; Nikonova, E.

114. Induction of species-typical 50 kHz vocalizations by dopaminergic agents injected into the lateral septum in the rat. Silkstone, M.; Brudzynski, S.M.

115. Presynaptic CaMKII regulates short-term plasticity via syntaxin. Igarashi. M.; Watanabe,Y.; Katayama, H.; Manabe, T.; Takao, K.; Miyakawa, T.

116. Mitragynine impaired one-trial inhibitory avoidance task in rats. Suhaimi, F.W. [Travel Award]; Hassan, Z.; Navaratnam, V.; Müller, C.P.

117. Noradrenergic transmission enhancement during memory consolidation and reconsolidation induces fear generalization as a matter of contextual conditioning intensity in rats. Gazarini, L.; Stern, C.A.J.; Carobrez, A.P.; Bertoglio, L.B.

118. Morphological effects of memory erasure and disruption of memory reconsolidation in Aplysia californica. Glanzman, D.L.; Chen, S.; Cai, D.; Sun, P.

119. Hypothermia, bradycardia and regional c-Fos expression induced by peripheral oxytocin: Evidence for vasopressin 1A receptor involvement. Hicks, C.; Ramos, L.; Hunt, G.E.; Jorgensen, W.; Dampney, B.; Misagh, G.H.; Kassiou, M.; McGregor, I.S.

120. MK-801, but not Ifenprodil, disrupts fear expression and extinction. Thomas, B.L.; Novak, C.; Hanna, M.; Harakas, M.

121. Age-dependent differences in the persistence of cocaine-induced conditioned activity in adult and young rats: Regional differences in Fos immunoreactivity. McDougall, S.A.; Pipkin, J.A.; Der-Ghazarian, T.; Cortez, A.M.; Gutierrez, A.; Lee, R.J.; Carbajal, S.M.; Shaddox, J.L.; Crawford, C.A.

122. A familiar conspecific is more effective in social buffering of conditioned fear responses in male rats. Kiyokawa, Y.; Honda, A.; Takeuchi, Y.; Mori, Y.

123. Relief conditioning: Behavioral characterization and neural basis. Fendt, M.

124. Temporal object memory in mice and the role of histamine 1 receptor. Zlomuzica, A. [Travel Award]; Dere, E.

125. T-type Ca2+ channels, Cav3.1, in GABAergic neurons of the medial septum are critical in regulation of hippocampal theta oscillations and behavior response to novelty. Gangadharan, G.; Shin, H.-S.

126. The rapid effects of the G-protein coupled estrogen receptor in the hippocampus on learning and memory in female mice. Lymer, J.; Gabor, C.; Phan, A.; Magahay, A.; Baines, N.; Choleris, E.

127. Non-genomic enhancing effects of estrogens on learning are mediated through ERα in the hippocampus. Phan, A.; Suschkov, S.; Molinaro, L.P.; MacLusky, N.J.; Choleris, E.

128. Estrogen receptor agonists have rapid and differential effects on social learning in female mice. Ervin, K.; Mulvale, E.; Boyd, J.; Montini, G.; Melendez, A.; Choleris, E.

129. Dopamine and memory: Involvement of hippocampal dopamine D1-type receptor in the social transmission of food preferences in male and female mice. Matta, R., Tiessen, A.N.; Choleris, E.

130. Differential role of glutamatergic mechanisms of the medial hypothalamus on the expression of unconditioned and conditioned fear responses. Reimer, A.E.; de Oliveira, A.R.; Brandão, M.L.

131. Mineralocorticoid receptors in the ventral tegmental area regulate dopamine efflux in the basolateral amygdala during the expression of conditioned fear. de Oliveira, A.R.; Reimer, A.E.; Brandão, M.L.

132. Non genomic effects of corticosterone influence fos protein expression in the prefrontal cortex and expression of contextual fear conditioning in rats. Reis, F.M.C.V.; Almada, R.C.; Fogaça, M.V.; Brandão, M.L.

133. Heparan sulfate deficiency in autistic postmortem brain tissue from the subventricular zone of the lateral ventricles. Corley, M.J. [Travel Award]; Pearson, B.L.; Vasconcellos, A.; Blanchard, D.C.; Blanchard, R.J.

134. Male monkeys (Cebuslibidinosus) behave differently according to the hormonal fluctuations of female reproductive cycle? Rodrigues, R.C.; Gasbarri. A.; Tomaz, C.; Tavares, M.C.H.

135. Bed nucleus of the stria terminalis CRF1, but not CRF2, receptors mediate the expression of contextual fear conditioning. Hott, S.C.; Gomes, F.V.; Uliana, D.L.M.; Resstel, L.B.M.

136. Fear Conditioning in Adult Zebrafish (Danio rerio). Vira, D.; Blaser, R.E.

137. Study of the expression of GluR1 and GluR2 in hippocampus of rats after injury by NMDA and evaluation of the neuroprotective effect of Parawixina 10. Fachim, H.A.; Pereira, A.C.; Iyomasa, M.M.; dos Santos, W.F.; Rosa, M.L.N.M.

138. Effects of exercise reward on spontaneous and amphetamine-induced appetitive ultrasonic vocalizations in rats. Heyse, N.; Álvarez, G.; Brenes, J.C.; Schwarting, R.K.W.

139. Dopamine depletion in dorsomedial or dorsolateral striatum impairs egocentric Cincinnati water maze performance while sparing allocentric Morris water maze learning. Williams, M.T.; Braun, A.A.; Amos-Kroohs, R.M.; Udobi, K.C.; Skelton, M.R.; Vorhees, C.V.

140. Cortical motor dominance and movement-related cortical potentials associated with finger force production. Chiang, H.-H.

141. Spatial learning in the plus-maze discriminative avoidance task: Role of proximal and distal cues and CA1 activity. Leão, A.H.F.F.; Medeiros, A.M.; Apolinário, G.K.S.; Cabral, A.; Ribeiro, A.M.; Barbosa, F.F.; Silva, R.H.

142. Carnivore urine and its component 2-phenylethylamine (PEA) activate the brain fear circuitry and elicit defensive behavior in rats. Wernecke, K.; Vincenz, D.; Goldschmidt, J.; Fendt, M.

143. Sleep and navigation: Does sleep differentially modulate cognitive strategies of navigation? Kashyap, N.

144. Systematic assessment of learning phenotypes in mutant mouse lines using automated home cage analysis. Remmelink, E.; Loos, M.; Maroteaux, G.; Smit, A.B.; Verhage, M.

145. Intensity-dependent effects of background noise on motor learning and performance in mice. Nishijima, T.; Hosokawa, M.; Amemiya, S.; Kita, I.

146. Role of BDNF/TrkB-signaling in the acquisition and consolidation of fear memories. Endres, T.; Lessmann, V.; Schulz-Klaus, B.

147. The role of amygdala nuclei in the active vs. reactive threat responding. Martinez, R.C.R.; Gupta, N.; Lázaro-Muñoz, G.; Sears, R.; de Oliveira, C.C.; de Castro, M.C.; Fonoff, E.T.; Teixeira, M.J.; Otoch, J.P.; LeDoux, J.E.; Cain, C.K.

148. A single social defeat stress provokes short- and long-term anxiogenic-like effects in mice. Cipriano, A.C.; Gomes, K.S.; Nunes-de-Souza, R.L.

149. Increased manganese and iron-deficiency during development in rats affect locomotor responses following pharmacological challenge. Amos-Kroohs, R.; Bloor, C.; Guitierrez, A.; Hufgard, J.; Vorhees, C.; Williams, M.

150. Hippocampal BDNF mediates the recovery of chronic stress-induced spatial memory deficits in adult male rats. Ortiz, J.B.; Mathewson, C.M.; Hoffman, A.N.; Campbell, A.N.; Lorson, N.G.; Conrad, C.D.

151. Regional patterns of neuronal activation associated with nitric oxide synthase inhibitors using c-fos immunohistochemical localisation. Sherwin, E.; Gigliucci, V.; Walsh, R.; Harkin, A.

152. Impaired contextual fear extinction and novel object recognition memory in a chronic psychosocial stress mouse model of brain-gut axis dysfunction. Kennedy, P.J.; O'Mahony, C.; Clarke, G.; Dinan, T.G.; Cryan, J.F.

153. Social modulation of LiCl-induced "disgust" responses in rats. Cloutier, C.J.; Ossenkopp, K.-P.; Kavaliers, M.

154. Temporary inactivation of the rodent hippocampus: An evaluation of the current methodology. Gulbrandsen, T.; Sutherland, R.

155. Defensive behavior in an olfactory fear conditioning paradigm: Role of the hippocampus, the periaqueductal gray and the medial hypothalamus. Carobrez, A.; Kincheski, G; Pavesi, E.; Kroon, J.

156. Toxin-induced gustatory conditioning in rats: Examining toxin-nutrient trade-offs when ingesting a palatable solution containing small amounts of a toxin. Good, A.N. ; Kavaliers, M.; Ossenkopp, K.-P.

157. Female mice heterozygous for creatine transporter deficiency show moderate cognitive deficits. Hautman, E.R.; Kokegne, A.N.; Udobi, K.C; Williams, M.T.; Vorhees, C.V.; Skelton, M.R.

158. Correlations between performance in different designs of the stroop task performance and heart rate in young adults. Amaral, M.E.; Garcia, A.; Carvalho, C.; Tomaz, C.

159. Cortical activity and autonomic response during the performance in different conditions of mental. Carvalho, C.; Garcia, A.; Amaral, M.E.; Tomaz, C.

160. Estradiol enhances ingestion in female rats. Reid, L.D.; Reid, M.L.

161. Prenatal stress predisposes male rats to subordinate status but may facilitate adaptation to stressful social environments. Scott, K.; Smeltzer, M.; de Kloet, A.; Flak, J.; Krause, E.; Woods, S.; Sakai, R.

162. The effect of (-)-OSU6162 on premature responses in male Lister Hooded rats is dependent on the individual level of emotionality. Holst, S.; Alsiö, J.; Mar, A.; Fernando, A.; Goodlett, C.; Carlsson, A.; Everitt, B; Steensland, P.; Dalley, J.

163. TRPV1 mRNA expression within the brain of two rat strains differing in nociceptive responsivity. Madasu, M.K.; Okine, B.; Olango, W.M.; Roche, M.; Finn, D.P.

164. Conjugated equine estrogens impact cognition: Effects replicate in the Sprague-Dawley® rat. Hewitt, L.T.; Mennenga, S.E.; Koebele1, S.V.; Lavery, C.N.; Mendoza, P.K.; Bimonte-Nelson, H.A.

165. EEG brain mapping of sex differences during performance of tasks requiring inhibitory control mechanisms. Garcia, A.; Rego, A.; Arcela, A.; Tomaz, C.; Tavares, M.C.H.

166. Age-related differences in performance during an emotional visuo-spatial working memory task: An EEG study. Belham, F.S.; Rego, A.C.; Garcia, A.; Tomaz, C.; Tavares, Mª. C.H.

167. Influence of exercise on neurotrophin production, cognition, and mood. Bugatti, M.; Szuhany, K. L.; Otto, M.W.

168. What social defeat and restraint have in common? Motta, S.C.; Brunton, P.J.; Russell, J.A.; Canteras, N.S.

169. Contribution of muscarinic cholinergic receptors in the area postrema in conditioned odor aversion. Roldan-Roldan, G.

Saturday, June 29

8:30-10:30 **Symposium**: **Behavioural neuroscience in Ireland**. Chairs: **Andrew N. Coogan; Stella Vlachou.** *Tara Suite*

8:30 Psychoneuroimmunology of the circadian clock. Coogan, A.

9:00 GABAB1 receptor subunit isoforms modulate susceptibility and resilience to stress-induced changes in behaviour: Implications for gene x environment interactions in depression and anxiety disorders. O'Leary, O.

9:30 GABAB receptors in reward processes: The role of GABAB receptor positive modulators in nicotine dependence. Vlachou, S.

10:00 Measuring brain activity in freely-moving rats using electroanalytical methods. Kealy, J.

10:30-11:00 **Coffee/Tea Break.** *Tara Suite*

11:00-12:00 **Keynote: Jaap M. Koolhaas,** University of Groningen, The Netherlands.
The violent rat brain. *Tara Suite*

12:00-1:30 **Break**

1:30-3:30 **Travel Award Data Blitz**. *Tara Suite*

1:33 Administration of nimodipine during the sensitive period for brain sexual-differentiation leads to sex-specific behavioral effects in adulthood: Neurodevelopmental implications for depression. Arad, M. [Travel Award]; McCarthy, M.M.; Gould, T.D.

1:42 Knockdown of glutamate receptor interacting protein (GRIP) within the nucleus accumbens enhances reinstatement of cocaine seeking and alters synaptic plasticity. Briand, L.A. [Travel Award]; Kimmey, B.; Ortinski, P.I.; Huganir, R.L.; Pierce, R.C.

1:51 Inhibition of Ventral Pallidum Projection to VTA Blocks Cue-Triggered Cocaine Seeking. Mahler, S.V. [Travel Award]; Vazey, E.M.; Kaufling, J.; Bryan L.; Roth, B.L.; Aston-Jones, G.

2:00 Effects of fluoxetine in corticosterone-induced depressive-like phenotypes in postpartum and nulliparous females. Workman, J. [Travel Award]; Kitay, M.F.; Chow, C.; Galea, L.A.M.

2:09 Temporal object memory in mice and the role of histamine 1 receptor. Zlomuzica, A. [Travel Award]; Dere, E.

2:18 Regulation of arc through miR-495 as a potential mediator of cocaine motivation and extinction learning. Bastle, R. [Travel Award]; Pentkowski, N.; Turk, M.; Adams, M.; Berger, A.; Dado, N.; Smith, K.; Hammer, R.; Perrone-Bizzozero, N.; Neisewander, J.

2:27 Heparan sulfate deficiency in autistic postmortem brain tissue from the subventricular zone of the lateral ventricles. Corley, M.J. [Travel Award]; Pearson, B.L.; Vasconcellos, A.; Blanchard, D.C.; Blanchard, R.J.

2:36 Overactivation of muscarinic cholinergic receptors leads to long-term anxiogenic responses associated with hippocampal theta rhythm activity and HPA axis alterations. Hoeller, A.A. [Travel Award]; Spiga, F.; Lightman, S.L.; Collingridge, G.L.; Bortolotto, Z.A.; De Lima, T.C.M.

2:45 Chronic stress impacts nonassociative fear and alters amygdala-hippocampal functional network activation. Hoffman, A.N. [Travel Award]; Lorson, N.G.; Hanna, J.J.; Mazur, G.J.; Taylor, S.B.; Yahn, S.L.; Sanabria, F.; Olive, M.F.; Conrad, C.D.

2:54 Acute prosocial effects of peripherally administered oxytocin, MDMA and their combination in rats: A possible common mechanism of action involving the V1A receptor. Ramos, L. [Travel Award]; Hicks, C.; Kevin, R.; Caminer, A.; McGregor, I.S.

3:03 Epigenetic bidirectional rescue of extreme genetic predispositions to anxiety: Impact of CRH receptor 1 in the amygdala. Sotnikov, S.V.[Travel Award]; Markt, P.O.; Avrabos, C.; Malic, V.; Chekmareva, N.U.; Naik, R.; Sah, A.; Singewald, N.; Schmidt, M.; Eder, M.; Landgraf, R.

3:12 Mitragynine impaired one-trial inhibitory avoidance task in rats. Suhaimi, F.W. [Travel Award]; Hassan, Z.; Navaratnam, V.; Müller, C.P.

3:21 Vicarious social defeat induces depression- and anxiety-like behavior in adolescent mice and increases nicotine consumption. Warren, B. [Travel Award]; Alcantara, L.; Vialou, V.; Parise, E.; Iñiguez S.; Nestler, E.; Bolaños-Guzmán, C.

3:30-4:00 **Coffee/Tea Break**. *Tara Suite*

4:00-6:00 **Symposium: Impulsivity, compulsivity, and addiction.** Chairs: **Heather N. Richardson; Trevor W. Robbins**. *Tara Suite*

4:00 Prefrontal cortex inhibitory control of cocaine craving - implications for relapse prevention. Ahmed, S.H.

4:30 Molecular mechanisms underlying compulsivity in addiction. Hollander, J.; Jonkman, S.; Bali, P.; Kenny, P.J.

5:00 Adolescence, alcohol, and impulsive choice. Boettiger, C.A.

5:30 The contributions of impulsivity and compulsivity to the development of neuropsychiatric disorders such as addiction. Robbins, T.W.

6:00-7:00 **Business Meeting – Open to all members.** *Guttenberg Suite*

8:00-12:00 **Awards Banquet**. *Tara Suite*

Wednesday, June 26

8:30-10:30 **Symposium: Neurobiology and behavioral consequences of estradiol signaling in the brain. Chair: Robert Meisel**. *Tara Suite*

8:30 **Estradiol feminizes the female brain during a specific prepubertal period.** Julie Bakker, GIGA Neurosciences, University of Liege; Netherlands Institute for Neuroscience; Medical Psychology, Medical Center Free University Amsterdam. The classic theory on mammalian brain and behavioral sexual differentiation is that an organizational action of testosterone, secreted by the male's testes, controls male-typical aspects of brain and behavioral development whereas no active perinatal sex hormone signaling is required for female-typical sexual differentiation. Furthermore much evidence suggests that many, though not all, of the perinatal organizational actions of testosterone on the development of the male brain actually results from the cellular effects of estradiol formed via neural aromatization of testosterone. However, a default developmental program for the female brain has been criticized. Indeed, in a previous study, female aromatase knockout (ArKO) mice, which cannot convert androgen to estradiol, showed deficient male-oriented partner preference and lordosis behaviors in response to treatment with ovarian hormones in adulthood, raising the possibility that estradiol may contribute to the development of these female sexual behaviors. New studies in our laboratory now showed that administration of estradiol prepubertally (between postnatal days P15-P25) significantly enhanced the ability of ArKO female mice to display lordosis behavior in response to ovarian hormones administered later in adulthood whereas treatment with estradiol over an earlier postnatal period (P5-P15) had no such effect. These results provide new evidence for an organizing role of prepubertal estradiol in the development of neural mechanisms that control female-typical sexual behavior. The classic view that female-typical neural and behavioral differentiation proceeds in the absence of any perinatal sex hormone signaling must be revised.

9:00 **Estrogen receptor regulation of metabotropic glutamate receptor signaling in the female rat nucleus accumbens: Anatomical and behavioral changes underlying addiction.** Paul Mermelstein, Department of Neuroscience, University of Minnesota. In addition to activating nuclear estrogen receptor signaling, estradiol can also regulate neuronal function via surface membrane receptors. These actions are mediated by the direct association of estrogen receptors (ERs) activating metabotropic glutamate receptors (mGluRs). These ER/mGluR signaling partners are organized into discrete functional microdomains via caveolin proteins. Furthermore, post-translational palmitoylation of ERs are required for ER trafficking to the surface membrane. This coupling of membrane ERs to mGluRs is found across the nervous system, including in the hippocampus, dorsal striatum, cortex, hypothalamus, and dorsal root ganglion. These actions are typically sex-specific, occurring in female, but not male animals. We now find that ER/mGluR signaling is also prevalent within the female rat nucleus accumbens. Estradiol regulates the density of dendritic spines on the projection neurons of the nucleus accumbens. This alteration of neuronal structure by estradiol is dependent on activation of mGluRs. Further, we hypothesize that ER/mGluR signaling within the female nucleus accumbens underlies both the sex differences and estradiol action on the use of drugs of abuse. Sponsored by DA035008

9:30 **Membrane actions of estradiol in the regulation of female sexual behavior.** Paul Micevych, Department of Neurobiology, David Geffen School of Medicine, UCLA. Estradiol has both direct nuclear actions and membrane-initiated cell signaling. Arguably, the best studied estradiol action in the CNS is the induction of sexual receptivity. Although the neural circuits, neurochemistry, and steroid dependence have been well established, more recently, our understanding of the mechanisms of estradiol induction of sexual receptivity have expand. Our laboratory has uncovered a part of the lordosis regulating circuitry of the hypothalamus that mediates the initial, rapid response of estradiol controlling sexual receptivity. This arcuate nucleus (ARH) to medial preoptic nucleus (MPN) to ventromedial nucleus (VMH) pathway underlies a rapid, transient, estradiol-induced inhibition of lordosis which is ultimately necessary for full expression of sexual receptivity. The activation of this circuit is mediated through membrane estrogen receptor-α (mERα) transactivation of metabotropic glutamate receptor-1a (mGluR1a). Estradiol auto-regulates its own signaling by controlling trafficking of the mERα-mGluR1a complex to, and its internalization from the cell membrane. mERα-mGluR1a signaling underlies the activation of a novel protein kinase, PKCθ, in the ARH leading to the activation of POMC neurons and the release of β-endorphin activating MPN μ-opioid receptors. Estradiol membrane signaling also activates LIM kinase phosphorylating the actin depolymerizing agent, cofilin. Phospho-cofilin is deactivated and allows the formation of immature filapodial spines in the ARH, which mature over the next 20-48 hours. When estradiol-induced spinogenesis is blocked with cytochalasin D, which prevents actin polymerization, the expression of lordosis behavior is attenuated. These results demonstrate the importance of estradiol membrane signaling for neural circuit activation and morphological plasticity needed for sexual receptivity in the rodent.

10:00 **Effects of Female Sexual Experience on Neuronal Plasticity.** Robert L Meisel, Department of Neuroscience, University of Minnesota. In contrast to our detailed understanding of the neurobiology of the expression of sexual behavior, especially in rodents, much less is known about the neural regulation of its motivational components. We have used female hamsters to model motivational control and synaptic plasticity following sexual experience. Repeated

sexual experience has rewarding consequences that appear to increase the copulatory efficiency of sexual interactions with males. This same sexual experience produces a sensitized release of dopamine in the nucleus accumbens and a cascade of postsynaptic cellular changes in medium spiny neurons, primarily in the core of the accumbens. We find there is an increased coupling of dopamine D1 receptors to mechanisms regulating cAMP production. This leads to enhanced signaling events, including modulation of Fos proteins, which increases the density of dendritic spines on dopamine D1 expressing neurons in the core of the nucleus accumbens. Collectively these findings suggest a feed forward process through which the expression of sexual behavior is regulated in a way that promotes reproductive success. Sponsored by DA013680.

8:30-10:30 **Symposium: Circadian rhythm and sleep behavior in drosophila.** Chair: **Norio Ishida**. *Guttenberg Suite*

8:30 **Genetics of sleep: Using a Drosophila model to identify molecular underpinnings.** Amita Sehgal HHMI, Department of Neuroscience, University of Pennsylvania, Philadelphia. The fruit fly, Drosophila melanogaster, has served as an excellent model to decipher the genetic and molecular basis of many processes, including circadian rhythms. The molecular nature of the biological clock that drives a 24 hour rhythm in many processes, including rest/sleep, was elucidated in Drosophila. Based upon the success of the Drosophila model in identifying mechanisms that time behavior and physiology, we sought to use it to understand a specific circadian-regulated behavior, sleep. We showed that Drosophila rest is a sleep-like state, and are now using it to determine what drives the need to sleep, in other words the homeostatic regulation of sleep. The molecular and cellular networks underlying circadian and homeostatic regulation are distinct and yet they also intersect. Over the year, we and others have identified molecular components of the clock and also molecules required to transmit time-of-day signals form the clock to produce rhythmic sleep:wake. To identify genes involved in the homeostatic regulation of sleep, we conducted forward genetic screens for mutants with reduced sleep times. One such mutant, which we named sleepless (sss), shows a > 80% reduction in sleep amount. The sss gene encodes a glycosylphosphatidyl inositol (GPI) -anchored membrane protein that interacts with the potassium channel Shaker. We found that SSS is required for appropriate levels, appropriate subcellular distribution and optimal activation of Shaker. It also reduces C type inactivation of Shaker. In addition to affecting amount of the daily sleep, sss affects recovery following sleep deprivation, supporting the idea that it is required for sleep homeostasis. To identify mechanisms by which SSS drives sleep, we used an unbiased proteomic approach. This has led to the identification of new mechanisms underlying sleep. Together these studies are expected to lead to an understanding of how circadian and homeostatic regulation are integrated to produce sleep:wake cycles.

9:00 **Phosphorylation regulates multiple processes to keep circadian time.** Paul Hardin, Texas A&M University. Daily rhythms in behavior, physiology and metabolism are driven by cell-autonomous clocks that are set by environmental time cues, but maintain ~24h rhythms in the absence of environmental cues. Genetic and molecular analysis of circadian clocks in Drosophila and mice revealed that the timekeeping mechanism is based on transcriptional feedback loops, where transcriptional activators drive the expression of transcriptional repressors, which enter the nucleus and feedback to bind activators, thereby inhibiting transcription until the repressors are degraded to permit the next cycle of transcriptional activation. Although key components of these feedback loops have been identified, how they sustain rhythms with a period of ~24h is not well understood. Several processes within the feedback loop are regulated by the phosphorylation of clock components, including nuclear localization, transcriptional repression, and protein degradation. To understand how phosphorylation contributes to feedback loop progression, we have characterized phosphorylation sites on the feedback loop activator CLOCK (CLK) and undertaken an RNA interference (RNAi) knockdown screen to identify novel protein kinases and phosphatases that alter circadian period or rhythmicity. CLK has multiple Ser/Thr phosphorylation sites that, when changed to Ala, alter rhythmic behavior. Several kinases and phosphatases not previously known to play a role in circadian timekeeping have been identified, and their effects on circadian rhythms have been validated. The cellular, molecular, and genetic analysis of CLK phosphorylation and novel kinases/phosphatases that alter clock function will be presented.

9:30 **Molecular neurogenetics of biological rhythms in an intertidal crustacean.** Charalambos Kyriacou, (University of Leicester, UK), Lin Zhang (University of Leicester, UK), David Wilcockson (University of Aberystwyth, UK) Mick Hastings (Laboratory of Molecular Biology, Cambridge, UK) & Simon Webster (University of Bangor, UK). The marine isopod Eurydice pulchra inhabits the coastline and shows both circadian (~24 h) and tidal (~12.4 h) rhythms in behaviour and physiology. While a great deal is known about the molecular basis of the 24 hour clock, nothing is known about tidal rhythms beyond the study of their behavioural phenotypes. We asked whether the circadian genes in this organism were also involved in the tidal oscillator by identifying the canonical clock genes, disrupting their expression using a variety of means and observing how the two types of rhythms were (or were not) affected. Our results suggest a simple molecular and neurogenetic explanation for how circadian and tidal rhythms are generated in this organism.

10:00 **Molecular and behavioral approach to understand circadian mating behavior in Drosophila.** Norio Ishida1,2, Takahiro Suzuki11, Kazuki Sakata2, Kunpei Ito1,2, Pan Hui 2, Haruhisa Kawasaki 1 1 ISHIDA Group of Clock Gene, Dept. of Biomedical Research, National Institute of Advanced Industrial Science and Technology (AIST),

1-1-1 Higashi, Tsukuba 305-8566, Japan, 2 Institutes of Applied Biochemistry, University of Tsukuba, Ibaraki 305-8502, Japan,. Circadian clocks of Drosophila melanogaster motivate males to court females at a specific time of day. However, clock neurons involved in courtship rhythms in the brain of Drosophila remain totally unknown. The circadian locomotor behavior of Drosophila is controlled by morning (M cells) and evening (E cells) cells in brain, which regulate morning and evening activities, respectively. Here, we identified the brain clock neurons that are responsible for the circadian rhythms of the close-proximity (CP) behavior that reflects male mating motivation. Interestingly, the ablation or functional molecular clock disruption of E cells caused arrhythmic CP behavior, but that of M cells resulted in sustained CP rhythms even in constant darkness. In addition, the ablation of some dorsal lateral neurons (LNd) of E cells using neuropeptide-F (NPF)-GAL4 did not impair CP rhythms. These findings suggested that the NPF-negative LNds and DN1s of E cells include cells essential for circadian CP behavior in Drosophila. Furthermore, we presented that the amplitude of rhythmic close-proximity (CP) behavior was dampened in lower nutrition, and that some nutrients recovered lower amplitude to normal level. Genes to Cells (2010) 15, 1240–1248, Proc. Natl. Acad. Sci. USA (2001) 98, 9221–9225.

10:30-11:00 **Coffee/Tea Break.** *Tara Suite*

11:00-12:00 **Keynote: John F. Cryan, University College Cork, Ireland. Mind-altering microbes: Role of gut microbiota on brain and behavior.** *Tara Suite*

Mind-altering microbes: Role of gut microbiota on brain and behavior. John Cryan, University College Cork, Cork, Ireland. Recent years have witnessed the rise of the gut microbiota as a major topic of research interest in biology. Studies are revealing how variations and changes in the composition of the gut microbiota influence normal physiology and contribute to diseases ranging from inflammation to obesity. Accumulating data now indicate that the gut microbiota also communicates with the CNS--possibly through neural, endocrine and immune pathways--and thereby influences brain function and behaviour. Studies in germ-free animals and in animals exposed to pathogenic bacterial infections, probiotic bacteria or antibiotic drugs suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition and pain. Thus, the emerging concept of a microbiota-gut-brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders ranging from stress-related disorders including depression and anxiety to neurodevelopmental disorders such as autism spectrum disorders.

12:00-1:30 **Break**

1:30-3:30 **Symposium: Nicotine reinforcement and dependence: Neuroadaptations in stop and go signals.** Chair**: Nicholas W. Gilpin.** *Guttenberg Suite*

1:30 **The role of the interpeduncular nucleus in nicotine withdrawal.** Andrew R. Tapper, University of Massachusetts Medical School, Worcester, MA, USA. Anxiety is a prominent affective withdrawal symptom driving abstinent smokers to relapse, yet the neuroanatomical and molecular bases underlying the anxiogenic effects of nicotine withdrawal are unclear. Using behavioral, pharmacological, and imaging approaches in rodents, we have identified the interpeduncular nucleus (IPN) as a neuroanatomical substrate of nicotine withdrawal-induced anxiety. The anxiogenic effects of nicotine withdrawal could be precipitated by infusion of a nicotinic acetylcholine receptor antagonist into the IPN of nicotine-dependent, but not nicotine-naïve mice. Conversely, nicotine infusion into the IPN during spontaneous nicotine withdrawal reduced anxiety. As the stress neuropeptide, corticotropin releasing factor (CRF) has been implicated in anxiety, we assayed expression of CRF receptor 1 and 2 in the IPN. CRF1 receptors and to a lesser extent, CRF2 receptors were highly expressed in the IPN. Infusion of CRF into the IPN was anxiogenic in mice and this effect was more robust in nicotine-dependent animals. In addition, CRF1 receptors were upregulated after chronic nicotine exposure. During nicotine withdrawal, neurons within the IPN were activated. IPN infusion of a CRF1 but not a CRF2 receptor antagonist, blocked activation and alleviated withdrawal-induced anxiety. Resting-state functional connectivity analysis in awake rats revealed that the IPN is part of a network functionally connected to brain regions of both the HPA and extra-hypothalamic stress axis including the pituitary, hypothalamus, and amygdala. These data indicate that the IPN is a component of the CRF stress network that mediates anxiety during nicotine withdrawal.

2:00 **Habenular signaling in nicotine reinforcement.** Luis Tuesta, Christie D. Fowler, Qun Lu and Paul J. Kenny. The Scripps Research Institute - Florida, Jupiter, FL 33458, USA. In addition to its rewarding effects, nicotine also has noxious effects that trigger avoidance of the drug. Sensitivity to nicotine aversion plays a key role in regulating vulnerability to tobacco addiction. In contrast to the rewarding effects of nicotine, thought to be regulated by midbrain dopamine neurons, very little is known about the neurobiological mechanisms of nicotine avoidance. We recently demonstrated that α5-containing nicotinic acetylcholine receptors (nAChRs) regulate activation of medial habenula (MHb) neurons that project to the interpeduncular nucleus (IPN). Moreover, MHb-IPN activation contributes to nicotine aversion. Here, new data is presented demonstrating that nicotine activates a small population of neurons in the nucleus tractus solitarius (NTS) that synthesize the neuropeptide glucagon-like peptide 1 (GLP-1). Mice with null mutation in GLP-1 receptors were more sensitive to nicotine reward and consume greater quantities of the drug than wildtype mice. GLP-1 receptors are densely expressed in the IPN. Using optical and electrical stimulation and electrophysiological

recordings, we show that GLP-1 receptor activation increases glutamate transmission in IPN slices. Accordingly, nicotine-induced IPN activation is diminished in GLP-1 receptor knockout mice. Moreover, stimulation of GLP-1 receptors in IPN blocks the rewarding properties of nicotine and profoundly decreases nicotine intake, whereas their blockade increases nicotine consumption of the drug. Finally, we show that dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for GLP-1 degradation, is expressed in IPN and the antidiatetic drug sitagliptin (Januvia), which inhibits DPP4, decreases nicotine intake. GLP-1 is therefore shown to control nicotine intake through actions on MHb-IPN aversion systems.

2:30 **Identification of CRF neurons in the VTA that control the aversive effects of nicotine withdrawal.** Olivier George. The Scripps Research Institute, La Jolla, CA. The corticotropin releasing factor (CRF) system has been hypothesized to counteract the positive rewarding effects of drugs of abuse mediated by dopamine neurons in the ventral tegmental area (VTA), through upregulation of CRF and activation of CRF1 receptor in the extended amygdala. This phenomenon is known as a between-system neuroadaptation that contributes to the transition to drug dependence. Here we show that a within-system neuroadaptation also occurs whereby previously unidentified CRF neurons in the VTA control the motivational effect of withdrawal. Using animal models of nicotine dependence, we show that CRF mRNA is upregulated after chronic exposure to nicotine, in a key part of the brain incentive salience/reward system, the dopaminergic neurons of the posterior VTA (pVTA). Moreover, upregulation of CRF mRNA, CRF release, and activation of CRF1 receptors locally in the pVTA during withdrawal directly control the motivational state elicited by nicotine withdrawal, thus linking the brain reward and stress systems within the same neurons in the pVTA.

3:00 **Nicotine Vapor Inhalation Escalates Nicotine Self-Administration.** Nicholas W. Gilpin, Ph.D., LSU Health Sciences Center, New Orleans, LA, USA. Humans escalate their cigarette smoking over time, and a major obstacle in the field of pre-clinical nicotine addiction research has been the inability to produce escalated nicotine self-administration in rats. In Experiment 1, male Wistar rats were trained to respond for nicotine in 2-hr operant sessions, then exposed to chronic intermittent (12 hrs/day) nicotine vapor and repeatedly tested for nicotine self-administration at 8-12 hrs withdrawal. Rats were tested intermittently on days 1, 3 and 5 of the vapor exposure procedure, then tested on consecutive days 6-15 of nicotine vapor exposure. Rats exhibited transient increases in operant nicotine responding during intermittent testing, regardless of vapor condition, and this responding returned to baseline levels upon resumption of consecutive-days testing (i.e., nicotine deprivation effect). Nicotine vapor-exposed rats then escalated nicotine self-administration relative to both their own baseline (~200% increase) and non-dependent controls (~3x higher). In Experiment 2, rats were exposed or not exposed to chronic intermittent nicotine vapor, then tested for spontaneous and precipitated somatic signs of nicotine withdrawal. Eight hrs following removal from nicotine vapor, rats exhibited robust mecamylamine-precipitated somatic signs of withdrawal. Chronic nicotine vapor also affected mRNA levels for nicotinic receptor subunits and corticotropin-releasing factor (CRF) in brain regions important for mediating nicotine self-administration and the aversive aspects of nicotine withdrawal. Collectively, these results suggest that chronic intermittent nicotine vapor inhalation produces somatic and motivational signs of nicotine dependence, the latter of which is evidenced by escalation of nicotine self-administration.

1:30-3:30 **Symposium: Social aggression.** Chair: **Newton Sabino Canteras**. *Tara Suite*

1:30 **Is short term potentiation the physiological basis of aggression escalation?** Potegal, M. University of Minnesota, Minneapolis, MN, USA. Anger can disrupt social functioning, but it is the escalation of angry aggression that leads to assault and homicide. Aggression escalation is rapid, automatic and powerful, so much so that it may well have specific physiological substrate(s). We hypothesize that Short Term Potentiation (STP) in the pathways known to subserve aggression is a main mechanism of escalation. Escalation in rodents can be measured in the well-established resident-intruder attack priming paradigm in which olfactory-vomeronasal exposure to, or actual physical attack on, a first, "priming" intruder reduces the latency and increases the number of attacks on a second, "probe" intruder. This attack priming effect lasts 30-90 min, consistent with STP duration. C-fos immunocytochemistry shows the medial amygdala (MeA) to be a key locus in the neural circuitry of attack priming. Conversely and crucially, brief, 200 Hz stimulation of MeA yields a priming-like escalation lasting 30 min. These are the same parameters that elicit STP, prompting our hypothesis that STP is the physiological basis of attack priming. MeA output activates the "hypothalamic attack area" (HAA) which organizes aggressive responses. A secondary hypothesis is that STP in MeA synapses is induced largely by olfactory-vomeronasal exposure and its role in priming may be to reduce initial attack latency. STP may also be induced in HAA synapses by actual attack; its role in priming may be to increase attack number or rate. A demonstration that behavioral attack priming increases a) postsynaptic potentials in the MeA elicited by olfactory tract stimulation and/or b) postsynaptic potentials in the HAA elicited by stimulating amygdalofugal pathways would be crucial evidence for the STP hypothesis.

2:00 **Ventral premammillary nucleus as a critical sensory relay to the maternal aggression network.** Newton Canteras, Department of Anatomy, Institute of Biomedical Sciences, University of Sao Paulo, Brazil. Maternal aggression is under the control of a wide variety of factors that prime the females for aggression or trigger the aggressive event. Maternal attacks are triggered by the perception of sensory cues from the intruder, and here we have identified for the first time a site in the hypothalamus of lactating rats that is highly responsive to the male intruder – the ventral

premammillary nucleus (PMv). The PMv is heavily targeted by the medial amygdalar nucleus, and we presently used lesion and immediate early gene studies to test our working hypothesis that the PMv signals the presence of a male intruder and transfers this information to the network organizing maternal aggression. PMv-lesioned dams exhibit significantly reduced maternal aggression, without affecting maternal care. The Fos analysis revealed that PMv influences the activation of hypothalamic and septal sites shown to be mobilized during maternal aggression, including the medial preoptic nucleus (likely to represent an important locus to integrate priming stimuli critical for maternal aggression), the caudal two-thirds of the hypothalamic attack area (comprising the ventrolateral part of the ventromedial hypothalamic nucleus and the adjacent tuberal region of the lateral hypothalamic area, critical for the expression of maternal aggression), and the ventral part of the anterior bed nuclei of the stria terminalis (presently discussed as being involved in controlling neuroendocrine and autonomic responses accompanying maternal aggression). These findings reveal an important role for the PMv in detecting the male intruder and how this nucleus modulates the network controlling maternal aggression.

2:30 **Hunting for an aggression locus in mice.** Dayu Lin, NYU School of Medicine, New York, NY, USA. Electrical stimulation of certain hypothalamic regions in cats and rodents can elicit attack behavior, but the exact location of relevant cells within these regions, their requirement for naturally occurring aggression and their relationship to mating circuits have not been clear. Here we show that optogenetic, but not electrical, stimulation of neurons in the ventromedial hypothalamus, ventrolateral subdivision (VMHvl) causes male mice to attack both females and inanimate objects, as well as males. Pharmacogenetic silencing of VMHvl reversibly inhibits inter-male aggression. Detailed analysis of electrophysiological recording in the VMHvl revealed that activities of VMHvl cells are dominated by male conspecific olfactory cues, reflective of attack movement related velocity, influenced by attack history and predictive of future attack. Furthermore, aggression related VMHvl cells preferentially form coactivation clusters both in the presence and absence of a male intruder. We thus suggest that a set of intrinsically connected VMHvl neurons transform the male specific sensory cues to aggressive motivation which leads to social approach and aggressive actions.

3:00 **Adolescent social stress in rats: Adult behavioral and neurobiological consequences**. Bauke Buwalda, Caroline M. Coppens, Julia van Drunen, and Jaap M. Koolhaas. Behavioral Physiology, University of Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands. Stressful events during early development are playing an important role in programming the brain for later life. There is a large number of studies suggesting that adverse conditions during pre- and postnatal development are predisposing risk factors for adult mood and anxiety disorders. Although the mechanisms behind these lasting effects are not fully comprehended it is, considering the high speed of development of the brain during this period of life, not very surprising that these detrimental effects can occur. Human studies indicate that adversity during puberty and adolescence also is a risk factor for the ontogeny of adult emotional and behavioral problems such as anxiety and depression but also anger and aggression. Changes in reproductive hormone system and remodeling of neuronal networks may play a role in this. A number of animal studies show that behavioral, neuroendocrine and neurobiological stress responses are increased in adolescent individuals when compared with adults. In our studies we exposed male adolescent rats repeatedly to the resident-intruder paradigm where they were confronted with highly aggressive adult wild-type Groningen resident males. We noticed that these socially defeated rats showed behavioral and physiological responses to various challenges at adult age that differed from that in non-stressed individuals. Since the Wistar rat strain is a highly domesticated rodent species which is very placid and docile we considered it likely that the Wistar rat is having reduced social skills in comparison with a wild rat. This may be one of the reasons that a Wistar rat responds in a rather strong way to a stressor like social defeat. Therefore, we also studied adolescent wild-type Groningen (WTG) rats (Rattus norvegicus) in this paradigm. These animals show a large individual differentiation in their social and aggressive behavior. Adolescent WTG rats were much less affected by repeated social stress of defeat in their behavior indicating that large individual differences exist in the vulnerability to develop stress pathologies later in life. Finally, we are exploring to what extent adolescent individuals really have an increased vulnerability in comparison with adults to develop lasting negative consequences of social as well as non-social stressors. We aim to present these new findings at the meeting in Dublin.

3:30-4:00 **Coffee/Tea Break**. *Tara Suite*

4:00-6:00 **Symposium: The endocrine disrupting compounds: What they are, where they are and how they change behavior. Chair: Cheryl S. Rosenfeld**. *Guttenberg Suite*

4:00 **Effects of endocrine disruptors on sexually selected behavioral traits.** Cheryl S. Rosenfeld, University of Missouri, Biomedical Sciences Department and Bond Life Sciences Center Investigator, Columbia, MO, USA. Sexually selected traits include those that facilitate competition with members of the same sex over mates (intrasexual competition) and discriminative choice of mating partners (intersexual choice), and many of these traits are programmed by developmental exposure to steroid hormones. In polygynous deer mice (*Peromyscus maniculatus*), selection for home range expansion during the breeding season has resulted in males exhibiting greater spatial navigational abilities than females. We hypothesized that this male behavior would be susceptible to developmental exposure to BPA. Consistent with our predictions, BPA-exposed male deer mice demonstrated diminished spatial abilities and exploratory behavior. Moreover, females engaged in less contact with BPA-exposed males than controls. Another *Peromyscus* species, the

California mouse (*P. californicus*) displays both social and genetic monogamy. No selection for sex differences in spatial learning and memory are apparent in California mice. Rather, male mate guarding and territorial defense are sexually selected traits in these males. California male mice developmentally exposed to BPA, however, demonstrate reduced territorial marking relative to unexposed males. BPA exposure had no effect on spatial navigational skills in either male or female California mice. In California mice, both parents provide important parental care. However, females, whose offspring was fathered by BPA-exposed males, spent less time nursing his pups. Moreover, BPA-exposed male and his control female partner spent less time in the nest and grooming the pups compared to control pairs. In summary, developmental exposure to BPA can compromise later adult behaviors in a species and sex-dependent manner. By using a socially monogamous animal model, we have the first evidence that developmental exposure to BPA can compromise both paternal and maternal behaviors. Comparative animal models that display contrasting reproductive behaviors might allow for sex-specific predictions regarding which behaviors are sensitive to the effects of BPA, and thereby provide a framework for human risk assessment studies. This work was supported by RC1 ES018195, a Mizzou Advantage Grant, and University of Missouri CVM Faculty Award to CSR.

4:30 **Prenatal bisphenol A impairs social memory and alters juvenile social behavior over multiple generations.** Jennifer T. Wolstenholme and Emilie F. Rissman Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, USA, 22908. Bisphenol A (BPA) is an environmental endocrine disrupting compound found in plastics, canned food linings and thermal receipts. Given that humans born after 1950 have been steadily exposed to low levels of BPA from the time they were conceived, we have undertaken a trans-generational behavioral and epigenetic study in the mouse to understand the effects of BPA on social behavior. At doses commonly found in human blood, BPA trans-generationally changes juvenile peer-to peer social interactions and persistently decreases oxytocin (Oxt) and vasopressin (Avp) mRNA in embryonic brain. We hypothesize that in utero BPA exposure causes persistent, epigenetically tractable alterations in the brain and these changes influence social behaviors. Further, BPA's epigenetic actions may differentially affect germline methylation leading to persistent changes in future generations. Female C57BL/6J mice were fed phytoestrogen-free chow with or without low dose BPA throughout pregnancy. Blood levels of BPA exposed dams were similar to levels reported in humans. Mice bred to the F3 generation and were tested for social and novel object recognition as juveniles. In the BPA lineage, F1 and F3 mice displayed significant delays in habituation to a familiar female. The effect was prolonged in the F3 mice. Social recognition was also impaired in F3 BPA exposed males. Recognition of a novel object was not different between any of the groups. We also report the ability of BPA to affect methylation and expression of candidate genes involved in social behavior, such as Esr1, Oxt and Avp. We find that prenatal exposure to low dose BPA has immediate and long lasting effects on brain transcription and social behaviors. Such heritable effects of an endocrine disrupting compound underscore the importance for considering gene-environment interactions in the origin of complex neurobehavioral diseases. Support NIH-MH086711 & Autism Speaks#4802 (EFR) and F32ES019404 (JTW).

5:00 **Environmentally relevant concentrations of endocrine disrupting compounds can disrupt amphibian mating behavior.** Hoffmann, F.[1]; Kloas, W.[1,2] [1] Leibniz-Institute of Freshwater Ecology and Inland Fisheries, Berlin, Germany; [2] Humboldt-University Berlin, Berlin, Germany. Endocrine disrupting compounds (EDC) accumulate in surface waters, thus, aquatic vertebrates such as fishes and amphibians are main targets of a vast number of compounds which adversely affect development and physiology. Although EDC are assumed to contribute to the worldwide decline of amphibian populations by adverse effects on sexual differentiation, evidence for EDC affecting amphibian mating behavior is lacking so far. In this study, we investigated whether the male mate calling behavior of the South African clawed frog (*Xenopus laevis)* is affected by environmentally relevant concentrations of (anti)estrogenic and (anti)androgenic EDC and whether this endpoint might be used as biomarker for the assessment of such EDC. To address this issue, male *X. laevis* were exposed to various concentrations of androgenic, antiandrogenic, estrogenic and antiestrogenic EDC. A detailed analysis of calling parameters was developed to allow for identifying the specific modes of action of EDC as well as to determine levels of sexual arousal of males. Additional tests were performed to reveal the biological relevance of EDC exposure of *X. laevis.* The present study demonstrates that even environmentally relevant concentrations of (anti)androgenic and (anti)estrogenic EDC can adversely affect the male mate calling behavior of *X. laevis.* Moreover, such effects might even result in reduced reproductive success of exposed animals. The immediate onset and the persistence of the EDC impacts suggest that they might be due to fast and long term alterations in the central vocal-motor pathway located in the central nervous system.

5:30 **Effects of an endocrine disruptor on anxiety behaviour in fish - Examples from zebrafish and guppy.** Hallgren, S., Södertörn University, Stockholm, Sweden. Animal behaviours such as foraging, predator avoidance, migration, exploration and reproduction are all essential for the survival of the individual as well as the population. Behaviours are integrated end-points of several physiological factors affected by the biotic, social and a-biotic environment, and involves the central nervous system, muscular control, the different senses and a number of hormones. Anthropogenic chemicals released from e.g. agriculture, industrial production, forestry and sewage treatment may interfere with these physiological processes and ultimately cause disturbances in animal behaviour. Disruption of the endocrine system has caught much attention in aquatic toxicology, with much focus on disruption of reproductive behaviour and fertility of exposed fishes. However, mammalian examples suggest that the hormonal axis dealing with the coping of stress (Hypothalamo-Pituitary-Adrenal axis) also is very sensitive to endocrine disruptors. Tests examining

stress related behaviours such as fear, anxiety, shoaling and exploration have recently been developed for fish models such as zebrafish. These tests have been suggested as useful tools in development of new psychoactive pharmaceuticals but can also be applied to behaviour toxicology . Our studies using two of these behaviour tests, the novel tank diving test and shoaling test, on Zebrafish and Guppy show that low doses of the synthetic oestrogen Ethynylestradiol-17α can affect both anxiety and shoal adhesive behaviour of exposed fish. We suggest that in fishes the susceptibility to potent endocrine disruptors in stress related behaviours is equal to that of reproductive end-points.

4:00-6:00 **Symposium: Stop mechanisms in normal behavior and in obsessive compulsive disorder.** Chairs: **Kurt Hoffman; Henry Szechtman.** *Tara Suite*

4:00 **The end to uncertainty – Yedasentience in normal and abnormal behavior.** Henry Szechtman (McMaster University) and Erik Z Woody (University of Waterloo). For many problems that require resolution, the environment or logic dictate the solution. But for issues where the concerns are future events, there is no definite resolution because future circumstances are inherently uncertain and thus neither logic nor the environment can dictate the precise solution. Nevertheless, despite this uncertainty, we routinely take actions and make decisions pertaining to future circumstances, probably because of some biologically available mechanism(s). That such mechanisms must exist is demonstrated most vividly by psychopathologies (such as OCD or brain lesions) that alter how the individual regulates behavior directed specifically toward future concerns. In this presentation, we will discuss the proposal that the mechanism that brings closure to uncertainty regarding potential threats is an internally generated "feeling of knowing" (termed "yedasentience") produced through engagement in certain species-typical behaviors, and that OCD is a psychopathology of yedasentience. Both animal and human studies will be considered.

4:30 **Starting and ending phases in motor behavior: The delimiters of pragmatism and stereotypy.** David Eilam, Hila Keren and Joel Mort. Department of Zoology, Tel-Aviv University, Israel. Motor behaviors that are common in daily life include two components: (i) pragmatic acts that are compulsory for task completion; and (ii) non-pragmatic acts that seem irrelevant for task completion. In terms of the sequential order of performance, pragmatic acts converge at the center of the task, preceded and followed by non-pragmatic acts. The preceding non-pragmatic acts construct a 'warm-up' phase ramping-up attentional focus for the performance of the pragmatic phase of the task. The non-pragmatic acts that follow the pragmatic phase construct a 'cool-down' phase of relaxation from the task and diminishing the concentration involved in performance. The temporal sequence of starting phase, pragmatic phase, and ending phase is fundamental in the process of shaping motor routines and rituals and in conveying the observer a sense of rigidity in task performance. Specifically, a pragmatic phase could comprise just a single act, yet when preceded and followed by starting and ending phases (respectively), the entire performance takes the shape of a stereotyped motor routine or ritual. In other words, we perceive a task as stereotyped due to the fixed temporal order of the phases (starting, pragmatic, and stopping) together with the inflexibility and commonality of the pragmatic acts. This impression of task stereotypy is not affected by the non-pragmatism of the starting and ending phases. Altogether, both the pre- and post-pragmatic phases serve as a 'cognitive pause' surrounding the performance of pragmatic motor tasks and shaping their form.

5:00 **What can studies of behavioural control in rats tell us about human stopping?** Eagle, D, University of Cambridge, UK. The ability to stop an action is dependent on a number of behavioural control processes. Diseases and disorders of the brain, that result from altered function of cortex or basal ganglia, often describe symptoms that represent fundamental impairments in stopping and behavioural control. I will present a summary of how we can use rodent models of cognitive features of behavioural inhibition to gain insight into the mechanisms that underpin behavioural control in human disorders. In particular, I will focus on the neural processes that underlie stopping on the stop-signal task. I will describe how this has particular relevance to the pathology of compulsive disorders such as obsessive-compulsive disorder.

5:30 **The rabbit as a model system for studying stopping mechanisms involved in normal, adaptive behavior.** Kurt Leroy Hoffman and Rafael Rueda Morales. Universidad Autónoma de Tlaxcala - CINVESTAV, Mexico. What neural processes underlie the stopping of normal, goal-directed behavior, and how do externally-derived cues associated with task completion impact on internally-generated motivation, in order that stopping occurs? The European domestic rabbit (Oryctolagus cuniculus) presents an experimentally-accessible opportunity to investigate these questions, as it displays several adaptive, species-specific behaviors that are maintained across a predictable and extended period of time, until the appropriate outcome is reached. We describe two such behaviors: Maternal nest building and the scent-marking of objects with the chin gland ("chinning"). Nest building involves the repeated collection of dry grass and carrying it back to the nest burrow. The duration of this behavior is determined both by the rabbit's perception of whether or not the nest is complete, as well as by the effort the rabbit spent performing the behavior. By contrast, the "turning on and turning off" of chinning appears to involve mechanisms of sensitization and habituation to visual or tactile characteristics of the objects being marked. Thus, the motivational drive to perform these behaviors is modulated by internally-generated and externally-derived cues. We present pharmacological data relevant to neurotransmitter systems involved in the maintenance and stopping of these behaviors, and argue that studying natural, adaptive behaviors such as these could lead to important insights into neural mechanisms underlying obsessive compulsive disorder.

6:00-8:00 **Break**

8:00-10:00 **Poster Session 1: Animal models of behavioral disorders.** *Guttenberg Suite*

1. **Behavioral correlates of risky decision-making and executive functions**. Shimp, K.G., Beas, B.S., Mitchell, M.R., Bizon, J.L., Setlow, B. University of Florida, Gainesville, FL, USA. Risky decision making is a part of daily life, but can be aberrantly expressed in psychopathological processes. Our lab has developed a rodent model of risky decision making (the "Risky Decision making Task", RDT) in which rats make choices 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). Behavior in this task has been shown to vary individually (i.e. different rats display low, medium, or high risk preferences) and these individual differences are stable across months of re-testing. (Simon et al. 2009; 2011) The goal of this experiment was to determine the contributions of distinct forms of executive function to these individual differences in risk taking, as well as to determine the relationship between risky and "impulsive" decision making. Male Long Evans adult rats (n=16) were first evaluated for their degree of cognitive flexibility (using an attentional set shifting task) and working memory (using a delayed response task). Rats were then tested on the RDT, and,finally, on a delay discounting task to assess impulsive decision making. Bivariate correlations among performance measures in the different tasks revealed the following: 1) Rats characterized as risk averse in the RDT made significantly more perseverative errors on the set-shifting task than did their risk-taking cohorts; 2) RDT performance was not related to working memory; 3) Delay discounting showed only a slight correlation with RDT performance. In addition, rats with steeper delay discounting (greater impulsive choice) showed corresponding poorer performance in the working memory task. Together, these results suggest that cognitive inflexibility appears to be a hallmark feature of risk aversion. Furthermore, impulsive choice is associated with poor working memory.

2. **Administration of nimodipine during the sensitive period for brain sexual-differentiation leads to sex-specific behavioral effects in adulthood: Neurodevelopmental implications for depression**. Michal Arad1, Margaret M. McCarthy1,2,3,4, Todd D. Gould1,2,4,5 1 Department of Psychiatry, 2 Program in Neuroscience, 3 Departments of Physiology, 4 Department of Pharmacology, 5 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 diagnosis of bipolar disorder and depression. CACNA1C codes for Cav1.2, which is an L-type voltage-gated calcium channel α1 subunit. Recently, we reported that Cacna1c haploinsufficiency in the mouse alters depression- and anxiety-like behaviors in a sex-dependent manner. Given that male and female haploinsufficient mice share reduced levels of Cav1.2, but differ in their behavior, our aim was to assess whether a blockade of Cav1.2 during a sensitive period for sexual differentiation of the brain will lead to a similar sex-specific behavioral pattern. To that end, male and female C57BL/6J mice received bilateral intracerebroventricular (0.25µl/side) injection of vehicle, 0.025µg/0.25µl or 0.25µg/0.25µl of nimodipine (Cav1.2 blocker) on postnatal day (PND) 0. A forth group of male and female mouse pups did not receive any injection. At adulthood (>PND77), all mice were tested in behavioral procedures that assess depression- and anxiety-related behaviors, cognitive performance, and spontaneous or amphetamine-induced locomotor activity. Neonatal administration of nimodipine did not affect cognitive performance (Y-maze), locomotor activity (Open Field; OF), or anxiety-related behavior (Elevated Plus Maze, OF) in adults. Depressive-like behavior (Forced Swim Test, Learned Helplessness) was modulated in a sex- and dose-dependent manner: in females the low dose increased while the high dose decreased depression-like behavior, whereas no effect was observed in the males. Increased locomotion in response to amphetamine was observed only in females treated with the low dose of nimodipine. These findings provide further support for the sex-dependent role of L-type calcium channels in the development of depression, suggesting that neonatal changes in activity of L-type calcium channels alters 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 mechanism underlying sex-specific risk for mood disorders.

3. **Chronic corticosterone treatment enhances operant extinction-induced despair and impairs HPA-axis activity as a function of age**. M. Komorowski, B. Topic, V. Lamounier-Zepter, J.P. Huston. Heinrich Heine University Duesseldorf, Germany. Withdrawal and the avoidance of former desirable situations are common symptoms of a major depression and likely appear as a consequence of a lack of reinforcement. In animal studies, we showed that despair-like behaviors can be induced by extinction of escape behavior (Morris water maze), as well as of positively reinforced operant behavior (Skinner-box) and proposed extinction-induced despair as a new animal model of depression. In an elongated operant chamber, extinction of food-rewarded behavior led to spatial avoidance of the former source of reward (feeder). Chronic treatment with the antidepressants citalopram and clomipramine attenuated extinction-induced avoidance behavior, suggesting that such behavior reflects a depressive-like state. To further investigate the scope and sensitivity of extinction-induced despair as an animal model of depression, we here treated adult (3-4 months old; n=12) and aged (18 months old; n=15) male Wistar-rats chronically with corticosterone (CORT) via drinking-water over a period of three weeks prior to extinction of cued food-reward (fixed interval 30 seconds) in the elongated operant chamber. Chronic treatment with corticosterone has been shown to induce a depressive-like phenotype. Treatment with CORT led to an increase in withdrawal

behavior in the aged rats during extinction compared to the control group and significantly decreased the time spent at the feeder. Additionally, all animals underwent a restrain-stress procedure with blood-sampling, where plasma ACTH- and corticosterone-levels were determined over three hours. Both, CORT-treated aged and adult rats had lower baseline levels of plasma ACTH and corticosterone compared to controls. The treatment significantly impaired the corticosterone response to the acute stressor, but did not affect the regression. The enhancement of withdrawal behavior by chronic treatment with CORT further supports the hypothesis that withdrawal serves as a sensitive marker for extinction-induced depression in the rat and might be of importance, especially for the investigation of late-life depression.

4. **Sex has limited influence on manic-like behavior of Black Swiss mice**. Ene H, Kara NZ, Einat H. School of Psychological Sciences, Tel-Aviv University and School of Behavioral Sciences, Tel Aviv-Yaffo Academic College, Israel. The lack of efficient animal models for the manic pole of bipolar disorder is a major factor hindering the research of its pathophysiology and the development of improved drug treatments. We previously demonstrated that the Black Swiss (BS) strain of mice is advantageous as an model animal for mania. Compared with other strains, male BS mice show low anxiety-like behaviors (risk taking), high preference for sweet solution (reward seeking), high aggression, low immobility in the forced swim test (vigor), and a high response to amphetamine (sensitivity to psychostimulants). Moreover, male BS mice are sensitive to mood stabilizers as their manic-like behaviors were ameliorated by lithium and valproate and had low levels of frontal cortex beta-catenin. Yet, the entire body of data regarding Black Swiss mice as a model of mania was obtained with males. Because sex plays an important role in the area of neuropsychopathology, the present study was designed to compare the behavior of male and female Black Swiss mice in tests relevant to mania. Mice were tested for spontaneous activity in the open field, sweet solution preference, elevated plus-maze, social interaction, forced swim test and amphetamine-induced hyperactivity. Results show that for most tested behaviors there are no behavioral differences between male and female Black Swiss mice except some indications for increased anxiety or reduced risk taking in the female mice. It is therefore suggested that the effects of sex on the behavior of BS mice is limited to very few behavioral domains.

5. **Increased monoamine transporter activity plays an important role in pro-inflammatory cytokine-induced anhedonia**. F. van Heesch, J. Prins, G.A.H. Korte-Bouws, K.G.C. Westphal, B. Olivier, A.D. Kraneveld, S.M. Korte; Division of Pharmacology, Utrecht University, The Netherlands. Evidence points to a role for pro-inflammatory cytokines in the pathogenesis of depression. A core symptom of major depression is anhedonia, i.e. the inability to experience pleasure. Based on literature and our latest findings, we hypothesize that pro-inflammatory cytokine-induced anhedonia is accompanied by an increased activity of monoamine transporters. Tumor necrosis factor-alpha (TNF-α) or lipopolysaccharide (LPS) were intraperitoneally injected to activate the immune system of mice and rats. To demonstrate that pro-inflammatory cytokines induce anhedonia, both mice and serotonin transporter knockout (SERT −/−) rats were tested in the intracranial self-stimulation (ICSS) paradigm. Furthermore, to demonstrate the involvement of monoamine transporters, in vivo microdialysis experiments before and after an LPS injection were performed in the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC) of SERT −/− rats as well as in mice pretreated with the triple monoamine reuptake inhibitor DOV 216,303 followed by an LPS injection 30 min later. ICSS data revealed that both TNF-α and LPS induce anhedonia in mice and rats. However, LPS-induced anhedonia was abolished in SERT −/− rats. Pro-inflammatory cytokine-induced anhedonia was associated with increased monoamine metabolite formation (5-HIAA, DOPAC and HVA) in the NAc and mPFC, pointing to increased activity of monoamine transporters. The formation of 5-HIAA was less high in SERT −/− than SERT +/+ rats exposed to LPS. In mice, DOV 216,303 completely or at least partly prevented LPS-induced metabolite formation in the NAc and mPFC. Collectively, these data support our hypothesis that increased SERT activity, and possibly a general increase in monoamine transporter activity, is important in pro-inflammatory cytokine-induced anhedonia.

6. **GABAergic signaling alterations contribute to impaired working memory in aged F344 rats.** Authors: C. Bañuelos[1], B. S. Beas[1], J.A. McQuail[2], R.J. Gilbert[1], B. Setlow[3], J.L. Bizon[1] Affiliation: [1]Department of Neuroscience, [3]Department of Psychiatry, The University of Florida College of Medicine, Gainesville, FL, [2]Program in Neuroscience, Wake Forest University, Winston-Salem, NC. Impairments in working memory functions supported by the prefrontal cortex (PFC) are a common feature of normal aging. Working memory critically involves GABAergic signaling in PFC; yet, surprisingly little is known about GABAergic alterations in PFC normal aging or whether such changes contribute to age-associated impairments in working memory. To investigate this, young adult (7 mo) and aged (25 mo) male F344 rats were characterized on an operant-based delayed response test of working memory. Rats were required to remember the location of a sample lever over a delay period (0-24 s) to obtain a food reward. Aged rats performed comparably to young at no delay but exhibited deficits relative to young at long delays. Immunoblots of PFC homogenates showed that the GABA synthesizing enzyme GAD67 was increased but the transporter important for reuptake of GABA after synaptic release (GAT-1) was decreased in aged PFC. GABA(B) receptor (GABA(B)R) expression was also reduced in aged PFC and was inversely related to working memory performance among aged rats. We next tested whether reducing GABA(B)R activation could improve working memory in impaired aged rats. Systemic injections of CGP55845 (0.1 mg/kg), a

GABA(B)R antagonist, enhanced performance in aged rats and these effects were mimicked by microinjections of CGP55845 into PFC. Together, these data suggest that age-related dysregulation of GABAergic signaling in PFC may play a causal role in impaired working memory and that targeting GABA(B)Rs may provide therapeutic benefit for age-related impairments in executive functions. Funding Source: NIH R01 AG029421 McKnight Brain Research Foundation

7. **Not presented.**

8. **White matter fractional anisotropy and social impairments in children and adolescents with autism**. Noriuchi, M.(1,2,3); Kikuchi, Y.(2); Kamio, Y.(3). 1 Dept. of Dementia and Higher Brain Function, Tokyo Metropolitan Institute of Medical Science; 2 Div. of Human Health Sciences, Graduate School of Tokyo Metropolitan University; 3 Dept. of Child and Adolescent Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry. Prior studies have suggested that abnormal neural connectivity may be responsible for dysfunctional higher information processing such as social communication in autism spectrum disorder (ASD). The white matter structure of ASD, however, is poorly understood. We used diffusion tensor imaging (DTI) to investigate white matter structure and its relationship with social behavior in high-functioning children and adolescents with ASD. We conducted a voxel-based whole brain DTI analysis to examine fractional anisotropy (FA), lambda 1, 2 and 3 in seven high-functioning children and adolescents with ASD and seven age-, gender-, handedness-matched healthy controls. Next, we investigated whether DTI parameters were associated with the severity of autistic symptoms measured by the Social Responsiveness Scale (SRS) which can quantify socio-communicative and other impairment. We found that FA or lambda 1 in the ASD group was significantly lower than controls in the rostral anterior cingulate cortex (ACC), the left dorsolateral prefrontal cortex (DLPFC), superior temporal/temporo-parietal junction, and the right temporal pole, amygdala, superior longitudinal fasciculus, occipitofrontal fasciculus and the rostral posterior ACC, and the mid- and left-anterior corpus callosum (aCC) which play an important role in social cognition and information integration by cortical connectivity. In addition, the total SRS score was negatively correlated with the FA value in DLPFC. Another major finding was the significantly increased lambda 1 in the cerebellar vermis lobules.

9. **The influence of age on the visual side-bias of pigeons (Columba livia)**. Debbie M. Kelly, University of Manitoba, Canada. Humans (Homo sapiens), pigeons (Columba livia) and chicks (Gallus gallus) over-attend to objects located on the left side of space. This pseudo-neglect likely reflects a right hemispheric specialization for spatial attention. For humans, this is typically tested using cancellation tasks in which participants cross-out characters printed on a sheet of paper placed in front of them. In an adapted version, birds sample grains arranged in a regular pattern. The neural organization underlying pseudo-neglect may be similar in both humans and birds; the right hemisphere processes a more bilateral representation of space, whereas the left hemisphere processes more right-sided visuo-spatial information. However, little is known about the hemispheric distribution of attention across the life-span. For humans, spatial attention is known to be especially vulnerable to aging effects, and important models predict a reduction of hemispheric specialization as well as an increase in individual variability with age. To test the impact of aging on spatial attention we used young (30 days), adult (3-5 years) and aged (9+ years) homing pigeons in an adapted version of the cancellation task. The birds could freely choose grain spread evenly over an area in front of them. The body was restrained and aligned centrally in front of the choice area, but the head could move freely. Adult pigeons showed a strong leftward bias, preferring to choose grain on the left side of space, hereby confirming previous findings in this species. However, young and aged birds showed a different pattern with more individual variation; indeed some individuals over-selected grains on their right side. Maturation processes of the young brain as well as compensatory mechanisms during aging will be discussed.

10. **Maternal separation-induced hypoactivity in the open field is reversed by exercise in male but not female rats: Effects accompanied by changes in orexin function**. M. H. James1,3, E. J. Campbell1,2,3, H. N. Richardson4, D. M. Hodgson2,3 & C.V. Dayas1,3 1School of Biomedical Sciences and Pharmacy, University of

Newcastle, Australia; 2School of Psychology, University of Newcastle, Australia; 3Centre for Translational Neuroscience and Mental Health Research, HMRI; 4Department of Psychology, University of Massachusetts, Amherst, USA Background: Early life stress (ELS) predisposes humans to psychopathology in later life. Recent preclinical evidence implicates the orexin system in some of these behavioural disturbances. Here, we examined the effects of maternal separation (MS), a common rodent model of ELS, on the expression of stress-related behaviours and orexin cell activation following restraint in adulthood. We also investigated whether any observed effects of ELS on these parameters can be reversed by voluntary exercise. Methods: Male and female rat pups were removed from dams for 0 or 3hrs on postnatal days (PND) 2-14. A subset of MS animals was allowed access to exercise wheels for 1h/day from PND40-73. On PND75, animals were exposed to restraint and then tested in the open-field apparatus (OF). Rats were then perfused and brains were dual-labelled for Fos-protein and orexin. Blood was collected to assess corticosterone levels. Results: Male and female MS animals exhibited decreased exploratory behaviour in the OF and elevated corticosterone levels. This was associated with a decrease in the percentage of Fos-positive orexin cells in the perifornical area of the hypothalamus and a decrease in total orexin cell numbers in the lateral hypothalamus in males. Exercise reversed MS-induced changes in behavior and corticosterone levels in males but not females. Exercise also prevented hypoactivity of orexin cells in males. Conclusions: MS results in dysregulated behavior in response to adult stress that is associated with hypoactivity of orexin cells. These findings are consistent with suppressed activity of the orexin system in animal models of depression and in patients with depressive disorders. Interestingly, changes associated with MS were reversed by voluntary exercise in males only, suggesting that the effects of exercise are sex-specific under these conditions.

11. **Interactive effect of serotonin deficiency, early life stress and maternal presence on corticosterone response to a psychosocial stressor.** Priddy, W. Department of Biology and Chemistry, Azusa Pacific University, Azusa, CA 91702-7000. Herod, SM. Department of Biology and Chemistry, Azusa Pacific University, Azusa, CA 91702-7000. Individual differences in stress sensitivity may be influenced by factors such as biogenic amine signaling, stress exposure and maternal presence. Here we examine the effects of low serotonin availability in mice exposed to early life stress (ELS) on corticosterone (CORT) response to psychosocial stress in adolescence, and persisting into adulthood. B6.129(Cg)-Slc6a4tm1KpI/J mice (SERT-WT, HET, and KO) were assigned to one of four treatment groups. "ELS+" animals experienced restraint stress for 3h/d, for 3 consecutive days between P22-P28, while control animals ("ELS-") were kept in their home cage with at least one littermate. To examine potential mitigating effects of maternal presence, a third group ("ELS+Mom") experienced identical restraint stress with the mother, unrestrained, in the test cage. In order to determine that such factors were specific to the maternal relationship, a fourth group experienced this same stressor with a novel adult female in the test cage ("ELS+Fem"). Maternal presence trended towards partially mitigating CORT response when compared to ELS+ mice across all genotypes ($p=.10$). Interestingly, ELS+Fem mice had a greater CORT response than ELS+ and ELS+Mom mice ($p=.025$), suggesting that the decreased CORT response of ELS+Mom mice was specific to the maternal relationship, and that the presence of the novel female had a potentially adverse effect. Despite higher baseline CORT levels, the response to adolescent psychosocial stress alone (ELS+) was blunted in KO mice compared to the HET and WT mice ($F=8.84$, $p=.05$). Differences in adolescent response to stress between animals with varying serotonin availability did not persist into adulthood. Ongoing studies examine this interactive nature of hyposerotonemia and early life stress in neurobiological and behavioral development.

12. **Epigenetic bidirectional rescue of extreme genetic predispositions to anxiety: Impact of CRH receptor 1 in the amygdala.** Sotnikov SV, Markt PO, Avrabos C, Malic V, Chekmareva NU, Naik R, Sah A, Singewald N, Schmidt M, Eder M, Landgraf R. Max Planck Institute of Psychiatry, Munich, Germany. The continuum of physiological anxiety up to psychopathology is not merely dependent on genes, but is orchestrated by the interplay of genetic predisposition, gene x environment and epigenetic interactions. Accordingly, inborn anxiety is considered a polygenic, multifactorial trait, likely to be shaped by environmentally-driven plasticity at genomic level. Here we tested whether and how beneficial vs. detrimental environmental manipulations are capable of rescuing anxiety phenotype. Animal studies suggest that environmental enrichment (EE) and unpredictable chronic stress (UCS) are promising ways of manipulating endophenotypes of psychiatric disorders. We succeeded in shifting the phenotypes of our >40 generations inbred high (HAB) and low (LAB) anxiety-related behavior mice towards "normal" anxiety, indicating the potential of EE and UCS to rescue even robust genetic predispositions. Our electrophysiological and c-fos expression studies indicate critical role of amygdala in reversing of anxiety phenotype. Next we were interested in studying genes, mediating behavioral shift, and found Crhr1 as a key player. We analyzed a series of possible regulatory mechanisms, which might cause the observed differences in Crhr1 expression level and identified differentially methylated CpG site (DMS) within the promoter region. Subsequent cell culture experiments proved functional relevance of this epigenetic modification on gene regulation. Moreover, transcriptional epigenetic factor YY1 is suggested to bind adjusted to DMS in methylation-dependent manner fine-tuning gene expression in differential environmental conditions.

13. **The genetic model of seizure states**. Fedotova I.B., Surina N.M., Poletaeva I.I., Biology Department, Lomonossov Moscow State University, Moscow, Russia, fedotova@protein.bio.msu.ru. The Krushinsky-

Molodkina (KM) rat strain is maintained in our Laboratory during 60 years, its inbred status being established by 1989. Audiogenic epilepsy (AE) in KM strain is characterized by high expressivity and of the trait. Several anticonvulsants effects were investigated using KM strain with decrease of AE proneness, so that this model could be used for preclinical assays of anticonvulsants. During many years Wistar rats (the initial population for KM selection) were used as the referent control group for study AE in KM rats, although the genetic background of KM strain inevitably accumulated numerous changes during 60 years of breeding apart from Wistars. In order to create the more reliable group of control animals which would share the larger part of genotype of AE susceptible KM rats the new selection experiment was initiated in 2001. The aim of this selection was to breed the strain of rats which are related to KM at least by a part of genotype but which would be non-prone to AE. The new strain was labeled as "0" strain. The genetic analysis of F2 hybrids postulated the two major genes inheritance with "modifiers" action. In F23 of "0" selection, the proportion of rats with total lack of AE was about 50%, the behavioral differences between KM and "0" strains were also found. The postictal and pinch induced catalepsy is also characteristic for KM rats as well as differences in DA and NMDA receptors in striatum. The high level of KM rats AE proneness, the possibility to compare KM to "0" strain and diverse types of experimental approaches could provide the important knowledge for the study of epileptogenesis. The work was supported by RFBR (grant N 12-04-00360-a).

14. **Cataleptic states of different origin, observing in Krushinsky-Molodkina (KM) rats, selected for audiogenic epilepsy proneness**. Surina Natalia, Lomonosov Moscow State University, Moscow, Russia. In intact rats of several genotypes with different predisposition to audiogenic epilepsy (KM, strains "0' and "4") the penetrance and expressivity of audiogenic postictal catalepsy (PC) correlated with the audiogenic fit (AF) intensity. In Long-Evans rats selected for AF and in WagRij rats this correlation was absent. The intensity of AF and PC was maximal in KM rat strain. The drug injections, which modulated the AF severity, levetiracetam and caffeine, confirmed this association. In the same time, phenazepam, afobazol, disocilpine and D-serine caused dissociation between AF parameters and the duration of the PC. Low doses of haloperidol induce rather intense catalepsy in rats of KM strain and in strains "4" and "0", while in Wistar and in Long-Evans rats the haloperidol-induced catalepsy was less prominent. The PC (after haloperidol) in these animals was not different from that before AF. The most marked «pinch» catalepsy (caused by multiple nape pinches) was observed in KM strain rats and strain «4» rats, these rats have the most marked predisposition to AF. This form of catalepsy did not develop in Wistar rats, WagRji and black-hooded rats, but it was revealed in 17% of strain «0» rats. «Pinch» catalepsy after sound exposure was revealed in all rats, demonstrating AF, except black-hooded rats. «Pinch» catalepsy was significantly increased in rats of strain «0», in which sound exposure did not lead to AF. All types of catalepsy studied were maximally expressed in KM rats.

15. **Vicarious social defeat induces depression- and anxiety-like behavior in adolescent mice and increases nicotine consumption.** Warren, B. Florida State University. Alcantara, L. Florida State University. Vialou, V. Mount Sinai School of Medicine. Parise E. Florida State University. Iñiguez S. Florida State University. Nestler, E. Mount Sinai School of Medicine. Bolaños-Guzmán C. Florida State University. It is well known that exposure to severe stress increases the risk for developing mood disorders. However, less is known about the complex interactions between witnessing and experiencing traumatic events. This study assesses the effects of a novel social stressor that is insulated from the effects of physical stress. Briefly, an adult male C57BL/6J mouse was socially defeated (PS) by a larger more aggressive CD1-mouse, while a second male C57BL/6J mouse witnessed this interaction from an adjacent compartment (ES). Ten days of exposure to ES induced long-lasting deficits in a battery of behavioral assays designed to assess changes in mood. Specifically, ES exposure increases sensitivity to anxiety- and stress-eliciting situations both 24 h and 1 month after witnessing physical stress. Increases in levels of serum corticosterone, a steroid hormone signaling stress response, accompanied these behavioral deficits. To determine whether ES exposure would increase consumption of nicotine, we gave mice access to nicotine during ES or PS. Interestingly, we found that ES and PS increased nicotine consumption. Interestingly, access to nicotine also normalized deficits in the social interaction test. Taken together, these data indicate that witnessing traumatic events is a potent stressor in adult male mice and that access to nicotine may protect adolescent mice from ES or PS induced deficits in social interaction.

16. **Exaggerated behavioural and HPA axis responses to stress in the non-obese diabetic (NOD) mouse**. Barry McGuinness1, Sinead M. Gibney1, Andrew Harkin2, Thomas J. Connor1, 1Department of Physiology & Trinity College Institute of Neuroscience, 2School of Pharmacy and Pharmaceutical Sciences & Trinity College Institute of Neuroscience, Trinity College, Dublin 2, Ireland. Both psychological stress and inflammation have been linked to the development of psychiatric illnesses including depression and anxiety. The non-obese diabetic (NOD) mouse is a model of autoimmune disease which was originally derived from the CD-1 mouse, and is characterised by the development of type-1 diabetes and autoimmune thryroiditis. In this present study the NOD mouse was used as a model to investigate the relationship between autoimmunity and stress-related behavioural and hypothalamic pituitary adrenal (HPA) axis disturbances. Behavioural testing in the open-field and elevated plus maze tests indicated heightened anxiety in NOD compared to CD1 mice. Following exposure to acute restraint stress (RS), NOD mice displayed a significant suppression of rearing and locomotor activity relative to CD1 mice, suggesting that they are more sensitive to stress than CD1 mice. NOD mice also demonstrated a prolonged corticosterone

response to stress, indicating impaired glucocorticoid feedback. Whilst stress failed to alter GR mRNA expression in the hypothalamus, GR mRNA expression in the hippocampus was reduced following stress in both CD1 and NOD mice, albeit to the same extent. Stress increased mRNA expression of the GR co-chaperone FKBP5 in both brain regions, and the stress-induced increase in FKBP5 was greater in NOD compared to CD1 mice. In contrast the GR chaperone HSP90 was not altered under basal conditions or in response to stress. Whilst inflammatory cytokines can promote glucocorticoid resistance, there was no evidence of increased mRNA expression of inflammatory cytokines (IL-1β, IL-6 or TNF-α) in the hippocampus of the NOD mice compared to the CD1 control strain. We suggest that the enhanced stress-related increase in FKBP5 expression observed in NOD mice could result in glucocorticoid resistance observed in this model. Supported by EUFP7 MOODINFLAME

17. **Stressor-induced IL-6 production and signalling: Divergence in responses between the periphery and CNS**. Barry McGuinness1, Sinead M. Gibney1, Andrew Harkin2, Thomas J. Connor1, 1Department of Physiology & Trinity College Institute of Neuroscience, 2School of Pharmacy and Pharmaceutical Sciences & Trinity College Institute of Neuroscience, Trinity College, Dublin 2, Ireland. IL-6 is a cytokine that is elevated in the plasma of depressed patients, and its production can be induced by psychological stress. Consequently IL-6 has been implicated in the pathogenesis of depression and other stress-related disorders. Studies to date have been limited to examining IL-6 production in response to stress, and have not examined the impact of stress on expression of other elements of the IL-6 system (receptors), or on IL-6 signalling either in the periphery or in the CNS. In fact the question remains as to whether the small quantities of IL-6 produced in the periphery in response to stress can impact upon the brain. Consequently, the aim of this study was to examine the impact of psychological stress on IL-6 production, IL-6 receptor expression, and IL-6 signalling in the periphery (liver) and brain (hypothalamus, hippocampus, cortex) in a mouse model. CD1 mice were killed either immediately or 2hr following a 2hr restraint stress. A robust increase in circulating IL-6 was observed following stress. In addition, stress increased circulating concentrations of the soluble IL-6 receptor; a molecule that permits IL-6 trans-signalling, and also induced mRNA expression of both subunits of the IL-6 receptor (IL-6R, and its signal transducer GP130) in liver. By contrast IL-6 or IL-6 receptor expression was not induced in the brain following stress. IL-6 signals via the JAK/STAT pathway activating STAT-3, and via the NF-IL-6 (C/EBPbeta) pathway activating C/EBPbeta. As an indicator of activation of these pathways we examined mRNA expression STAT-3, its downstream inducible gene SOCS-3, and also examined mRNA expression of C/EBPbeta. Stress induced a robust induction of STAT3, SOCS3 and C/EBPbeta expression in the liver. In contrast, stress failed to induce STAT3 or SOCS3 expression in brain, but did induce C/EBPbeta expression in all three brain regions, albeit to a much lesser extent than observed in the periphery. These data demonstrate that stress-induced IL-6 elicits a limited signalling profile in the brain relative to the periphery, with IL-6 signalling in the brain being restricted to a modest activation of the NFIL-6/ C/EBPbeta pathway.

18. **Not presented.**

19. **Simulated shift work and development of type 2 diabetes in mice**. Linda A. Toth and Rita A. Trammell, Departments of Pharmacology (Toth) and Internal medicine (Trammell), Southern Illinois University School of Medicine, Springfield IL 62794. Considerable epidemiologic evidence has linked shift work (SW) to increased weight gain, metabolic syndrome and increased risk of type 2 diabetes (T2D). We sought to test this relationship prospectively. Our hypothesis was that exposure to repeated diurnal phase shift mimicking SW would precipitate T2D in mice that were diabetes-resistant but at risk due to genetics, diet, or both. We tested this idea by using male NON/ShiLtJ mice, which have impaired glucose tolerance but do not normally progress to T2D. NON/ShiLtJ mice were weaned at 3 wks of age onto either a 4% or an 11% fat diet. At 8 wks of age, mice either remained on a stable 12:12 LD cycle or were switched to our SW paradigm. This intervention mimics the human experience of SW by imposing an initial delay in the anticipated rest phase (i.e., the work week), followed 5 days later by a comparable advance of the active phase (i.e., the weekend); the cycle then repeats. After 8 wks of exposure to SW or the stable LD cycle, mice were fasted for the last 5 h of the light phase, weighed, and killed by exsanguination under isoflurane anesthesia immediately before dark onset on day 2 of the "weekend". Among the normally T2D-resistant NON/ShiLtJ mice that had experienced SW, 40% (6 of 15) had fasting hyperglycemia >250 mg/dL,

independent of diet and without weight gain, as compared with no hyperglycemia >250mg/dL in the 16 non-SW mice ($p < 0.05$, Z-test). The hyperglycemia was coupled with a trend toward lower mean insulin levels in SW mice, suggesting the development of pancreatic β cell failure. We speculate that extending the duration of SW exposure would could signs of metabolic syndrome and precipitate T2D in a greater proportion of mice.

20. **c-Fos Up-Regulation Differences between the C57BL/6 N and J Mice Substrain in the mPFC Brain Region that is Related to Emotional Perseveration**. Landrau-Giovannetti1, S.; Sáez1, E., Peña de Ortiz2, S.; Méndez-Merced, A1. 1Universidad del Este, Escuela de Ciencias y Tecnología, Carolina, PR, USA 00984; 2Universidad de Puerto Rico, Departamento de Biología, Rio Piedras, PR, USA 00931. We use two C57BL/6 mouse substrains, J vs N, as animal models to study individual differences of recovery from Post-Traumatic Stress Disorder (PTSD). We noticed, from the Pavlovian Tone Fear Conditioning Paradigm, that J mice are good fear extinguishers while N mice are poor fear extinguishers. This impairment, of the N mice, constitutes a form of emotional perseveration since they have trouble in extinguishing fear. We want to address gene expression differences between these two mouse substrains within brain regions with extinction of the conditioned fear. We hypothesized that N and J mice display significant differences in the variation of genes that are related to learning and memory processes during the extinction of fear. Our previous study showed that the related levels of c-Fos mRNA within the amygdala of post-extinction trained N and J mice were significantly up-regulated when compared to naïve animals. For our present study we performed quantitative Real Time Polymerase Chain Reaction (qRT-PCR; Taqman Master Mix and Gene Expression Assay, Applied Biosystems) for CREB, Nurr-1 and c-Fos genes within the medial Prefrontal Cortex (mPFC) brain region. We ran four replicates of pooled (n=2) samples from naïve and post-extinction trained N and J mice. Quantifications of both targets (CREB, Nurr-1, c-Fos) and reference (β-actin) genes were done with the standard curve and comparative threshold, delta CT, methods (1.4 Sequence Detection 7300, Applied Biosystems). A statistical analysis was performed using Prism version 4.0 (Graph Pad software. Inc.), one-way ANOVA and Bonferroni's multiple comparisons test were used to assess the differences in mean, and standard error between the particular group pairs. Our results showed that the relative levels of c-Fos mRNA within the mPFC of post-extinction trained J mice were significantly up-regulated, $p<0.0001$, when compared to naïve animals, and experimental N mice. In this investigation we have collected data supporting the notion that both C57BL/6 mice substrains, N and J, display differences in the modulation of genes during fear extinction learning. This shows us that c-Fos is an important immediate early gene in response of the stimulus to fear and extinction of the previously learned fear. Supported by: NIMH 1SC1MH086072, MHDBSBRN-NIH IP20MD003355, and URGREAT-MBRS-RISE 2R25GM066250-05A.

21. **Neurodevelopmental effects of early life stress, serotonin deficiency and maternal presence on adulthood psychosocial behaviors.** Lewandowski, K. Herod, SM. Department of Biology and Chemistry, Azusa Pacific University, Azusa, CA 91702-7000. Individuals differ in the sensitivity to stress and susceptibility to develop a range of stress-induced behavioral disorders like anxiety, depression, and disordered social interaction, a common symptom of autism. Exposure to early life stress (ELS), disrupted functioning of serotonin, including low serotonin availability, and maternal presence are factors that may underlie the development of stress-sensitivity. The B6.129(Cg)-Slc6a4tm1KpI/J (SERT) mouse strain was used as a model of hyposerotonemia. At weaning (P21), SERT mice (WT, HET, and KO) were assigned to one of four treatment groups: exposure to early life stress (ELS+), stress in the presence of the mother (ELS+Mom) or a novel female (ELS+Fem), or no early life stress (ELS-). Stressed mice (ELS+, ELS+Mom, ELS+Fem) were restrained for 3h/d, for three consecutive days between P22-P28 while ELS- controls were left in their home cages with at least one littermate. In adulthood, behaviors in the light/dark box, Porsolt forced swim, and three-chamber social interaction tests were measured using the ANY-maze system (Stoelting Co., Wood Dale, IL). Across all treatment groups, HET and KO animals showed increased anxiety-like behavior during the light/dark box test ($F=3.79$; $p=0.05$), and decreased social behavior in the social interaction test as compared with WT littermates ($t=4.79$, $p=0.04$). Interestingly, ELS+ mice showed resiliency to depressive-like behavior in the forced swim test ($F=3.47$, $p=.05$), as well as increased social behavior ($t=15.00$, $p=0.04$) that was not seen in other stress groups (ELS+Mom or ELS+Fem). These preliminary findings suggest interactive and potentially neuroprotective effects of stress exposure in early adolescence with variations in serotonin functioning, though presence of the mother or a novel female during stress appears to be a critical factor in this developmental study.

22. **Effects of repeated fluoxetine and paroxetine exposure on anxiety-like behaviors**. Crawford CA, Humphrey DE, Powers C, Valentine JM; California State University, San Bernardino, CA, USA. Repeatedly treating adolescent rats with fluoxetine (FLX) or paroxetine (PAX) differentially affects anxiety-like behaviors when measured 24 h after the last drug treatment. Specifically, PAX, but not FLX, decreased time spent in the open arms of an elevated plus maze (EPM). The purpose of the present study was to determine the longevity and the robustness of this drug-induced change in affective behavior. Male and female Sprague-Dawley rats (n=9) were injected with PAX (2.5 or 10 mg/kg, ip), FLX (10 mg/kg, ip), or vehicle for 10 consecutive days starting on postnatal day (PD) 35. Rats were assessed for anxiety-like behavior using an EPM and a light-dark box. Behavioral testing occurred 24 h, 1 week, or 1 month after the last drug treatment (i.e., on PD 45, PD 52, or PD 73). When assessed 24 h after the last drug treatment, PAX (10 mg/kg) increased the anxiety of male rats as measured

on the EPM. When tested 1 week after drug discontinuation, the lower dose of paroxetine (2.5 mg/kg) increased time spent in the open arms (i.e., it decreased anxiety). Neither SSRI altered EPM performance when assessed 1 month after the last drug treatment. In the light-dark box, FLX increased the anxiety of male rats when tested 24 h and 1 week after drug treatment. Anxiety-like behavior was not altered in male rats 1 month after treatment. Neither PAX nor FLX affected the anxiety-like behaviors of female rats on either task. These data show that repeated treatment with PAX and FLX can affect anxiety-like behaviors for at least one week, but only in male rats. Moreover, these data indicate that the effects of these SSRIs on anxiety is dependent on the type of behavioral task used.

23. **Chronic stress impacts nonassociative fear and alters amygdala-hippocampal functional network activation**. Hoffman, AN; Lorson, NG; Hanna, JJ; Mazur, GJ; Taylor, SB; Yahn, SL; Sanabria, F.; Olive, MF; Conrad, CD. Department of Psychology, Arizona State University. Chronic stress may impose a vulnerability to develop maladaptive fear-related behaviors after a traumatic event. It is not clear how chronic stress affects contextual extinction following cued fear conditioning, or to a change in context after extinction. Male rats were subjected to chronic restraint stress (STR; wire mesh restraint 6h/d/21d) or undisturbed (CON), then tested on fear acquisition (3 tone-footshock pairings), and two extinction sessions (15 tones/session) within the same context. Then each group was tested (6 tones) in either the same context (SAME) or a novel context (DIFF), and brains were perfused for c-Fos immunohistochemistry. Compared to CON, STR showed facilitated fear acquisition, resistance to tone extinction on the first extinction day, and robust recovery of fear responses on the second extinction day. STR also showed robust freezing to the context when sampled prior to tone onset during the first extinction day. When tested in the same or a novel context, STR exhibited higher freezing to context than CON, suggesting that STR-induced fear was not dependent on context. Regardless of test context, STR showed greater c-Fos expression in the basolateral amygdala and CA1 of the hippocampus, which were negatively correlated in the STR-DIFF group, suggesting that chronic stress shifts limbic functional network activity during a fear memory. Greater c-Fos expression was also observed in the central amygdala in STR-DIFF vs. CON-DIFF. These data demonstrate that chronic stress enhances fear learning and impairs extinction, and affects nonassociative processes as demonstrated by enhanced fear in absence of the tone and in a novel context. This study provides insight into how a history of chronic stress affects behavioral and neural processing of a traumatic event, and may shed light on risk factors in the development of post-traumatic stress disorder. Funding sources: Arizona State University College of Liberal Arts and Sciences (Conrad), and NIDA R03DA032632 and NIMH R03MH094562 (Sanabria).

24. **Relaxin-3/RXFP3 neural networks and control of arousal- and stress-related behaviours**. Gundlach, A.L.; Ma, S.; Blasiak, A.; Smith, C.M.; Ganella, D.E.; Ryan, P.J.; Hosken I.T.; Lawrence, A.J.; Bathgate, R.A.D.; Olucha-Bordonau, F.E.. The Florey Institute of Neuroscience and Mental Health. Melbourne, Australia. Orexin and CRF peptides have established roles in the control of arousal and stress-related behaviours. In contrast, relaxin-3/(GABA) neurons in the nucleus incertus (NI) and midbrain, with widely distributed relaxin-3 fibres in brain areas rich in the relaxin-3 receptor, RXFP3, are not as well recognised for involvement in these processes. Early data revealed NI as a relay in septohippocampal networks linked to theta rhythm, exploration and cognition. NI/relaxin-3 terminals contact septohippocampal neurons and RXFP3 signalling in septum can modulate theta rhythm and spatial memory. NI/relaxin-3 neurons are activated by neurogenic stressors (e.g. restraint) and by food-anticipatory activity and exploratory activity [1,2]. More recent studies have identified novel aspects of relaxin-3/RXFP3 neurobiology. We have shown that NI/relaxin-3 neurons receive CRF and orexin inputs, and are activated by CRF and orexin A via CRF1 and OX2 receptors. We have identified a relaxin-3/RXFP3 pathway between the PAG and intergeniculate leaflet of rat thalamus, consistent with putative control of circadian activity and the phenotype of relaxin-3 KO mice. Acute central RXFP3 activation (icv) in male rats increased food intake and reduced anxiety in the elevated plus-maze and light-dark box. Chronic RXFP3 activation in hypothalamus, by a viral vector-driven RXFP3 agonist, increased daily food intake and body weight, possibly via regulation of oxytocin neurons. Current studies are examining mechanisms associated with these diverse RLN3/RXFP3 actions and the nature of interactions with stress, arousal and motivation circuits. 1. Ryan PJ et al. (2011) Neurosci Biobehav Rev 35, 1326-1341 2. Smith CM et al. (2011) J Chem Neuroanat 42, 262-275.

25. **Neurobiological effects of contingency training in male rats exhibiting predisposed coping strategies: Implications for depression.** Lambert, K.G.[1]; Hyer, M.M.[1]; Hazelgrove, A.[1] Rzucidlo, A.[1]; Bergeron, T.[1]; Bardi, M.[2] Dept of Psychology, Randolph-Macon College, Ashland VA USA 23005[1]; Dept of Psychology, Marshall University, Hungington WV USA 25755 [2]. Major Depression Disorder (MDD), characterized by diminished pleasure, motivation and goal-directed responses, ranks among the top ten global disease burdens. Considering recent reports of disappointing efficacy rates of antidepressant pharmaceutical approaches, a critical need exists for appropriate animal models to elucidate key neurobiological characteristics for the development of effective therapy options for MDD. Accordingly, in the current study, male rats were profiled using the back test previously used in our laboratory and were categorized as passive, active or flexible copers. Each coping group (n=12) was subsequently divided into a contingency-trained (C-T) or non-contingency trained (NC-T) group and, depending on the training assignment, was exposed to four weeks of either C-T or NC-T via Effort-Driven Reward training. Animals were subsequently trained in a spatial learning task (i.e., Dry Land Maze) so that problem solving

strategies in the final probe task, as well various markers of brain activation and plasticity (fos, doublecortin, BDNF), could be assessed. Additionally, fecal samples were collected during EBR training to determine stress responsivity (i.e., CORT and DHEA levels). Results indicated that C-T rats exhibited more adaptive responses in the probe trial (e.g., fewer freeze responses, fewer interrupted grooming sequences, and more targeted search strategies) than the NC-T rats; additionally, increased dentate gyrus doublecortin immunoreactivity (indicating increased numbers of developing neurons) and more adaptive CORT/DHEA ratios were observed in the C-T animals. Of the three coping profiles, flexible copers exhibited more adaptive responses than the more consistently responding active and passive copers. Thus, contingency training may provide neurobiological resilience against the emergence of behaviors consistent with MDD symptoms.

26. **Not presented.**

27. **Interaction of a dietary supplement with lithium in a rat model of mania.** McMillen, Brian A., Nagchowdhuri, Partha. S., Carr, Cara E., Cormier, Zachary A., Williams, Helen L. Brody School of Medicine, Greenville, NC, USA. Lithium salts have long been used to treat bipolar disorder. This disorder is difficult to model in rats, but one procedure uses rapid eye movement-sleep deprivation (REMsd) to induce spontaneous hyperactivity in rats that can be prevented by long-term treatment with Li+. A proprietary formulation of a nutrient supplement, EmpowerPlus (EP), was reported to reduce the needed dose of Li+ in bipolar patients. To test whether this is demonstrable in the rat model, Li+ alone in drinking water or combined with EP added to rat chow was given to rats for two weeks prior to a 3-day REM sleep deprivation period that used the "flower pot" method. After the rats were removed from the flower pots and placed in a standard cage, activity and time to quiescence were recorded for 45 min and then the animals were euthanized, brains removed and the medial prefrontal cortices (PFC) and corpus striatum (CS) dissected and retained for assay of dopamine (DA) and its metabolite, DOPAC by HPLC-ECD. REMsd increased activity by 76% in the first 10 min after removal from the flowerpots and by 63% for the full 45 min observation period. Addition of EP (equal to 0.2 capsules/day/rat) to the lab chow or presentation of 20 mM Li+ was without effect and combining the two resulted in a 15% decrease in activity from the REMsd only group (not significant). Compared to non-REMsd rats, concentrations of DOPAC in the PFC (0.21 ±0.03 vs 0.23 ±0.03 ug/g) and CS (3.75 ±0.46 vs 3.17 ±0.43 ug/g) were unaltered by REMsd or any of the treatments combined with REMsd. Although the REMsd model has been proposed as a model to study the effects of anti-manic drugs such as Li+ and other mood stablilizers, we were not able to demonstrate an effect.

28. **Not presented.**

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29. **Pro-social ultrasonic communication in rats: Social-communication deficits after post-weaning but not post-adolescence social isolation - phenotypic rescue by re-socialization**. Seffer, D. Rippberger, H. Schwarting, R.K.W. Wöhr, M. Behavioral Neuroscience, Experimental and Physiological Psychology, Faculty of Psychology, Philipps-University of Marburg, Marburg, Germany. Rats are highly social animals and rough-and-tumble play during adolescence has an important role for social development. Separation from conspecifics during this phase is known to impair social behavior. Post-weaning social isolation in rats is a widely used animal model to induce behavioral phenotypes and changes in neural development relevant to psychiatric disorders like schizophrenia (Fone & Porkess, 2008). Ultrasonic vocalizations (USVs) are an important component of the rat's social behavioral repertoire and serve as situation-dependent affective signals. 50-kHz USVs are produced in appetitive situations and induce social approach behavior, supporting the notion that they serve as contact calls (Wöhr & Schwarting, 2007). Here, we tested whether social isolation impairs approach behavior in response to playback of pro-social 50-kHz USVs and whether isolation-induced deficits depend on the time period of isolation during development. Male rats were either exposed to group housing (GH), short-term isolation for 24h (SI), or long-term isolation for 28 days (LI). Rats were isolated either as weanlings with 3 weeks of age or as post-adolescent young adults with 7 weeks of age, after going through rough-and-tumble play. We also tested for phenotypic rescue by exposing a subgroup of rats to one additional week of peer-rearing before testing. While GH and SI rats displayed social approach behavior in response to 50-kHz USVs, post-weaning LI lead to a pronounced deficit, since rats displayed avoidance rather than approach behavior. Such deficits were not observed after post-adolescence LI, indicating a critical period for social development during puberty. Importantly, social deficits induced by post-weaning LI were reversed by peer-mediated re-socialization, highlighting the importance of social experience for affiliative behavior.

30. **Antidepressant-like effects following single or repetitive NOS inhibitors administration in mice: Comparison with fluoxetine.** Rúbia M. W. Oliveira1, Vanessa M. S. Leal1, Vívian T. Bonassoli1, Humberto Milani1 and Elaine Del Bel2. 1State University of Maringá, Department of Pharmacology and Therapeutics, Av. Colombo 5.790, Maringá, Brazil. 2Faculty of Dentistry, University of São Paulo, Av. Bandeirantes, Ribeirão Preto, Brazil. e-mail: rmmwoliveira@uem.br. Nitric oxide synthase (NOS) inhibitors have been reported to present anxiolytic- and antidepressant-like effects in different experimental models. NOS inhibitors have also been proposed to impair exploratory behavior and induce catalepsy after systemic or intrastriatal injection in mice. Tolerance to cataleptic effects, however, have been observed within 4-5 days of continuous treatment with NOS inhibitors. Objective: To investigate whether repeated (7 days) administration of NOS inhibitors would interfere with its antidepressant-like effects in mice. Methods: Adult male Swiss mice (30-40 g) received i.p. injection of 7NI (50 mg/Kg), a selective neuronal NOS inhibitor, 1400W (1.5 mg/Kg), a selective iNOS inhibitor, fluoxetine (10 mg/Kg) a selective serotonin reuptake inhibitor or vehicle. A separated group of mice received previous intra-hippocampal injections of neurotoxin 5,7 dihidroxitriptamine (5,7DHT) before 7NI treatment in order to investigate whether the effects of 7NI was dependent of hippocampal serotonin. The treatments were performed by a single or by repetitive i.p. injections during 3 or 7 days. One hour after the last drug administration, the animals were tested in the forced swim test (FST). The immobility time was scored for each animal. Results: ANOVA showed that a single injection of fluoxetine or 7NI decreased the immobility time in the FST as compared to controls ($F_{3.34}=4.16$, $p=0.014$). No significant effect was detected with a single 1400W administration ($p>0.05$). Repetitive fluoxetine, 7-NI or 1400W administration lead to significant reductions on the immobility time (3 days= $F_{3.28}=6.12$, $p=0.029$; 7 days $F_{3.24}=4.52$, $p=0.014$). Previous intra-hippocampal injection of 5,7DHT prevented the anti-immobility effects of 7NI in the FST. Conclusions: Repetitive administration of the selective nNOS and iNOS inhibitors results in sustained antidepressant-like effects in the FST, similar to fluoxetine effect. The antidepressant-like effect of 7NI is dependent of hippocampal serotonin. Acknowledgments: UEM, CAPES and Fundação Araucária

31. **Chronic unpredictable mild stress alters an anxiety-related defensive response, Fos immunoreactivity and hippocampal adult neurogenesis.** JS de Andrade 1, RO Abrão 1, IC Céspedes 1, TB dos Santos 1, L Diniz 2, LRG Britto 3, RC Spadari-Bratfisch 1, D Ortolani 1, L Melo-Thomas 1, RCB da Silva 1, MB Viana1* 1Department of Biosciences, Federal University of São Paulo (UNIFESP), Santos, SP, Brazil. 2Department of Psychiatry, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil. 3Institute of Biomedical Sciences, Department of Physiology and Biophysics, University of São Paulo (USP), São Paulo, SP, Brazil. Previous results show that elevated T-maze (ETM) avoidance responses are facilitated by acute restraint. Escape, on the other hand, was unaltered. To investigate if the magnitude of the stressor is an important factor influencing these results, we investigated the effects of unpredictable chronic mild stress (UCMS) on ETM avoidance and escape measurements. Analysis of Fos protein immunoreactivity (Fos-ir) was used to map areas activated by stress exposure in response to ETM avoidance and escape performance. Additionally, the effects of the UCMS protocol on the number of cells expressing the marker of migrating neuroblasts doublecortin (DCX) in the

hippocampus and on corticosterone serum levels were investigated. Results showed that UCMS facilitates ETM avoidance, not altering escape. Avoidance performance increases Fos-ir in the cingulate cortex, hippocampus (dentate gyrus) and basomedial amygdala. Escape increases Fos-ir in the dorsolateral periaqueductal grey and locus ceruleus. In stressed animals submitted to ETM avoidance, increases in Fos-ir were observed in the cingulate cortex, ventrolateral septum, hippocampus, hypothalamus, amygdala, dorsal and median raphe nuclei. In stressed animals submitted to ETM escape, increases in Fos-ir were observed in the cingulate cortex, periaqueductal grey and locus ceruleus. Also, UCMS exposure decreased the number of DCX-positive cells in the dorsal and ventral hippocampus and increased corticosterone serum levels. These data suggest that the behavioral effects of UCMS are related to the activation of different sets of brain structures and confirms that this stress protocol activates the hypothalamus-pituitary-adrenal axis and induces neurodegenerative effects in the brain. Funding: FAPESP, Brazil (# 2011/17471-0).

32. **Evidence for behavioral sensitization to stress in rats using variations of the noise test.** Heyser, C.J., Rosen, M, and Yochum, C.L. Department of Neuroscience, University of California, San Diego, La Jolla, CA 92093, USA. White noise is commonly used in animal research as a background stimulus to mask extraneous auditory stimulation. Interestingly, white noise is also used as a stressor, with its effectiveness as a stressor being related to its intensity (dB) and unpredictability. In previous research, rats were exposed to a novel open field where the behaviors of each rat were assessed for 3 min before and 3 min during the presentation of a white noise (80 dB). Under these conditions, the rats significantly increased freezing during the second 3 min period (noise on) relative to the first 3 min period (no noise). The present series of experiments was conducted to further characterize this phenomenon in male Sprague Dawley rats. In Experiment 1, the order of noise presentation was varied ([no noise - noise - no noise] vs [noise - no noise - noise]). The results showed that the highest amount of freezing was observed during the second 3 min period in both groups. Thus, freezing appears to be elicited by changing stimulus conditions and not due to the presentation of noise per se. In Experiment 2, rats were repeatedly tested in the open field after an interval of 1 or 7 days under conditions described in Experiment 1. When testing was repeated at a 1-day interval, behavioral responses were characteristic of habituation. In contrast, when testing was repeated at a 7-day interval, a significant increase in freezing was observed after the stimulus change. The overall pattern of behavioral changes following a longer testing interval are taken as evidence for behavioral sensitization. These results with rats may provide a useful tool to elucidate mechanisms underlying behavioral sensitization to stress.

33. **Oldie but Goldie? Advanced paternal age increases the offspring's risk of developing neuropsychiatric phenotypes.** H. Rippberger[1], D. Seffer[1], T. Kircher[2], A. Krug[2], R.K.W. Schwarting[1], M. Wöhr[1] [1]Behavioral Neuroscience, Experimental and Physiological Psychology, Faculty of Psychology, Philipps-University of Marburg, Marburg, Germany [2]Department of Psychiatry and Psychotherapy, Philipps-University of Marburg, Marburg, Germany. Neuropsychiatric disorders, such as schizophrenia, are characterized by impairments in cognition, social behavior and communication. Schizophrenia is a common disease with a prevalence of 1 %. Its etiology is under high genetic influence with a heritability of 50-80%. In addition to genetic risk, there are environmental effects (e.g. high paternal age) and gene-environment interactions contributing to overall liability. While several genetic variants have been found to increase the risk of developing schizophrenia, little is known about the pathophysiology of environmental effects that lead to differential gene expression of relevant genes. However, despite the fact that epidemiological studies demonstrated an association between high paternal age and schizophrenia, the underlying causality is not yet understood since experimental evidence in humans is not feasible. The development of animal models that allow environmental and genetic confounds to be controlled is needed in order to establish causality between risk factors and brain pathophysiology. Here, we conducted a detailed and longitudinal study where we analyzed the offspring from male rats which had been either young adult or aged. The study, which is still ongoing, encompasses deep behavioral phenotyping, including ultrasonic communication, social play behavior, prepulse inhibition, amphetamine responsiveness, memory and anxiety. Furthermore, it is planned to investigate the effect of paternal age on gene expression in this rat model and to investigate the associated genetic variants in large cohorts of healthy human subjects. Preliminary data indicate that offspring of aged males display deficits in prepulse inhibition, a test of sensorimotor gating, and in the psychomotor responsiveness to the dopamine agonist amphetamine, that is, in two well established models of schizophrenia. These findings indicate that the effects of paternal age can also be studied in laboratory rats.

34. **Changes in cortical-brainstem functional connectivity during repeated social stress in mice**. Franklin, T.B.1; Vyssotski, A.2, Gross, C.1 1 EMBL Monterotondo, Monterotondo Italy; 2 University of Zurich/ETH Zurich, Zurich Switzerland. Functional imaging studies investigating the brains of affective disorder patients have suggested that stress-related mental illness may be the result of impaired top-down cortical regulation of emotion-centered brain areas. We hypothesized that stress-induced plasticity in cortical-brainstem connectivity may be a key causal factor in the development of stress-associated mental disease. To investigate this, recording electrodes were implanted in mice in a cortical area (the medial prefrontal cortex (mPFC)), and a brainstem area (the dorsal periaqueductal grey (dPAG)), and local field potentials were recorded during and following repeated social defeat encounters. We found that mice exposed to repeated defeats developed pronounced social anxiety behaviours, associated with reduced synchronous activity between the mPFC and dPAG. Interestingly, evidence for reduced

functional connectivity between the mPFC and the dPAG was also found in homecage conditions many hours after a single exposure to social defeat, suggesting that defeat encounters cause persistent changes in mPFC-dPAG connectivity that do not require the presence of a stressful stimulus to be elicited. This may represent a change in basic brain function that is likely to alter the overall behavioural strategy of the animal. Future work will determine the causal impact of manipulation of the direct connection between the mPFC-dPAG.

35. **Different temporal courses of motor and cognitive deficits in a progressive animal model of Parkinson's disease**. Santos, J.R.(1); Dierschnabel, A.L.(1); Campêlo, C.L.C.(1); Leão, A.H.F.F.(1); Macedo, P.T.(1); Silva, A.F.(1); Engelberth, R.C.G.J.(2); Cavalcante, J.S.(2); Abílio, V.C.(4,5), Izídio, G.S.(3); Silva, R.H.(1); Ribeiro, A.M.(1); (1)Memory Studies Laboratory, Physiology Department, Universidade Federal do Rio Grande do Norte, Natal, Brazil; (2)Laboratory of Neuroanatomy, Morphology Department, Universidade Federal do Rio Grande do Norte, Natal, Brazil; (3)Department of Cellular Biology, Embryology and Genetics, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil; (4)Department of Pharmacology, Universidade Federal de São Paulo, São Paulo, Brazil; (5)Laboratório Interdisciplinar de Neurociência Clínica (LiNC), Department of Psychiatry, Universidade Federal de São Paulo, São Paulo, Brazil. Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The main symptoms are motor (tremor, muscle rigidity and bradykinesia), cognitive (attention, recognition memory and executive function impairments) and emotional (anxiety and depression) alterations. Studies have shown that cognitive impairment may precede motor changes. However, animal studies are mostly conducted with an acute neurotoxin injection that leads to severe motor impairment, precluding the investigation of cognitive performance. We aimed to mimic the progressive nature of PD through the repeated administration of 6-hydroxydopamine (6-OHDA). Treatment on alternate days (i.c.v., 10 µg in 1.0 µl of 0.2% ascorbic acid) induced progressive motor deficits, as shown by catalepsy, oral movements and open-field tests. The treatment also induced memory deficit in the novel object recognition task, which appeared before the motor alterations. The rats also showed anxiety- and depression-like behaviors (decreased exploration of the open field center and reduced sucrose preference). These changes were accompanied by a progressive decrease of in tyrosine hydroxylase (TH) levels in the SNpc, ventral tegumentar area, locus coeruleus, dorsal striatum, prefrontal cortex and hippocampus. The alterations were still present 20 days after the last injection. The results indicate a possible application of repeated treatment with 6-OHDA in the study of the non-motor symptoms and the progressive nature of PD.

36. **Doxycycline restrains glia and confers neuroprotection in a 6-OHDA Parkinson model**. Marcio Lazzarinia,f, Sabine Martinb,c, Mišo Mitkovskic,d, Rita Raisman Vozarie, Walter Stühmerb,c* and Elaine Del Bela,f aDepartment of Morphology, Physiology and Pathology School of Odontology of Ribeirão Preto (FORP), University of São Paulo (USP), Ribeirão Preto, SP, Brazil; bDepartment of Molecular Biology of Neuronal Signals and dLight Microscopy Facility, Max Planck Institute of Experimental Medicine, Göttingen, Germany; cCluster of Excellence “Center Nanoscale Microscopy and Molecular Physiology of the Brain” (CNMPB), Göttingen, Germany; eINSERM, UMRS 975, CRICM, Experimental Therapeutics of Neurodegeneration, University Pierre & Marie Curie, Paris 6, Faculté de Médecine, CNRS, UMR 7225, Hôpital de la Salpêtrière, Paris, France; Paris. fDepartment of Neurology Medical School FMRP University of São Paulo (USP), Ribeirão Preto, SP, Brazil. Neuron–glia interactions play a key role in maintaining and regulating the central nervous system. Glial cells are implicated in the function of dopamine neurons and regulate their survival and resistance to injury. Parkinson's disease is characterized by the loss of dopamine neurons in the substantia nigra pars compacta, decreased striatal dopamine levels and consequent onset of extrapyramidal motor dysfunction. Parkinson's disease is a common chronic, neurodegenerative disorder with no effective protective treatment. In the 6-OHDA mouse model of Parkinson's disease, doxycycline administered at a dose that both induces/represses conditional transgene expression in the tetracycline system, mitigates the loss of dopaminergic neurons in the substantia nigra compacta and nerve terminals in the striatum. This protective effect was associated with: (1) a reduction of microglia in normal mice as a result of doxycycline administration per se; (2) a decrease in the astrocyte and microglia response to the neurotoxin 6-OHDA in the globus pallidus and substantia nigra compacta, and (3) the astrocyte reaction in the striatum. Our results suggest that doxycycline blocks 6-OHDA neurotoxicity in vivo by inhibiting microglial and astrocyte expression. This action of doxycycline in nigrostriatal dopaminergic neuron protection is consistent with a role of glial cells in Parkinson's disease neurodegeneration. The neuroprotective effect of doxycycline may be useful in preventing or slowing the progression of Parkinson's disease and other neurodegenerative diseases linked to glia function.

37. **Behavioral Characterization of Sindbis Virus Infected Mice**. Potter, MC.1; Baxter, VK.2; Wozniak, KM.1; Griffin, DE.2; Slusher, BS.1 1Brain Science Institute, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD 21205, USA; 2Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA. Sindbis virus is an alphavirus that infects neurons in mice causing acute viral encephalomyelitis. Hippocampal neurons and motor neurons are particularly vulnerable to infection. To date, behavioral deficits have not been characterized following sindbis virus infection in mice. In this study, we sought to identify motor, anxiety and cognitive deficits in sindbis virus infected mice at 5, 30 and 90 days post-infection. The mice were infected at 5-6 weeks of age with the TE strain of sindbis virus (106

PFU in 20ul of PBS) via intranasal administration. A battery of behavior tests were then performed on the mice including open field, elevated plus maze, Y-maze spontaneous alternation and both contextual and cued fear conditioning at each timepoint. In the open field test, sindbis virus treated mice were hyperactive and less anxious 5 days after infection but these characteristics were not observed at 30 or 90 days post-infection. Testing on the elevated plus maze confirmed these effects on anxiety at 5 days post-infection. On the Y-maze spontaneous alternation test, there was no difference between groups at any timepoint. At 5 days post-infection, the sindbis virus infected mice were severely impaired on both cued and contextual fear conditioning. Only contextual fear conditioning was impaired at the 30 day timepoint and, by 90 days, impairments in both contextual and cued fear conditioning were no longer present. In summary, sindbis virus infection seems to have an acute effect on motor, anxiety and cognitive abilities, all of which normalize over time. This represents a valid model of viral encephalomyelitis in which to test novel therapeutics for their ability to alter these functional outcomes.

38. **Different learning and memory performance in an APP/PS1 mouse model of Alzheimer's disease with chronically reduced BDNF**. Psotta, L.1, Rockahr, C.2, Veit, M.3, Kirches, E.3, Bock, J.2,4, Braun, A. K.2,4, Lessmann, V.1,4, Endres, T.1 1 Institute of Physiology, Otto-von-Guericke University, Magdeburg, Germany 2 Institute of Biology, Otto-von-Guericke University, Magdeburg, Germany 3 Institute of Neuropathology, Otto-von-Guericke University, Magdeburg, Germany 4 Center for Behavioral Brain Sciences (CBBS), Magdeburg, Germany. In Alzheimer's disease (AD) impairments of learning and memory processes are among the first disabilities which become apparent. These impairments get more severe with ongoing development of the disease. Increasing levels of Aβ protein are discussed to underlie the proceeding pathology of AD leading finally to the degeneration of neurons. Previous studies revealed that AD patients show - besides Aβ and tau pathology - also reduced levels of BDNF (brain-derived neurotrophic factor) within the brain and the blood serum. BDNF is an essential factor for synaptic plasticity and neuronal survival and thus a likely candidate to be involved in the mechanisms of AD pathology. We hypothesize that BDNF has a protective effect on Aβ affected neurons and that BDNF might influence Aβ accumulation. Thus, we expected that a chronic reduction of endogenous BDNF in a mouse model of AD would lead to an accelerated onset of AD symptoms and pathology. Therefore we created a new mouse model by crossbreeding heterozygous BDNF knock-out mice which exhibit a chronic 50% reduction of BDNF (BDNF+/- mice) with an AD mouse line (APP/PS1 mice, Radde et al., 2006). To analyze if these newly created APP/PS1-BDNF+/- mice exhibit an accelerated onset of AD symptoms, we tested these animals at different ages in the Morris Water Maze, the Shuttle Box, as well as in the Novel Object Recognition task. First results indicate age-dependent learning deficits in the active avoidance as well as in spatial learning, whereas short-term memory remains intact in all tested mouse lines. Besides the behavioral testing, we started to analyze the levels of BDNF as well as of Aß protein in different brain areas of the tested animals. Furthermore, we also started to analyze the mRNA expression of several important antioxidative enzymes in whole brain lysates of these mice.

39. **Anxiolytic-like effects exerted by serotonin at 5-ht2c receptors may be modulated by 5-ht3 receptors located within the mouse periaqueductal gray matter**. Canto-de-Souza, A.1,3,4; Lopes, L.T.1,4; Nunes-de-Souza, R.L.2,4; 1Dept Psychology-Psycobiology group/UFSCar, ²Pharmacol, FCF/Unesp/Araraquara, 3Graduate Program in Psychology/ UFSCar/São Carlos, 4Joint Graduate Program in Physiological Sciences UFSCar/UNESP, Brazil. Serotonin plays a dual role in anxiety: this monoamine may increase or attenuate anxiety, depending on the receptor subtypes (e.g., 5-HT1A, 5-HT2A,B,C, 5-HT3) and post-synaptic sites [e.g., amygdala, hippocampus, periaqueductal gray matter (PAG)] involved. In the PAG, while several studies have emphasized that serotonin exerts an anxiolytic/panicolytic-like effect at 5-HT2 receptors, little is known about its role at 5-HT3 receptors in anxiety-related responses. Here, we investigated the effects of intra-PAG injections of m-chlorophenylbiguanide (mCPBG) and ondansetron, respectively 5-HT3 receptor agonist and antagonist, on behavior of mice exposed to the elevated plus-maze (EPM). We also investigated whether the anxiolytic-like effect produced by intra-PAG injection of 1-(3-chlorophenyl) piperazine (mCPP), a preferential 5-HT2C receptor agonist, is changed with prior local injection of ondansetron. Anxiety was assessed by recording spatiotemporal (% open-arm entries and % open-arm time) and ethological (e.g., stretched-attend postures and head-dipping) measures, and locomotor activity by measuring the closed-arm entries. Intra-PAG ondansetron (0, 0.3, 1.0 or 3.0 nmol/0.1 µl) alone induced an anxiogenic-like effect only at the highest dose (Exp. 1). mCPBG (0, 40, 80 or 160 nmol/0.1 µl) alone did not alter any behavior in the EPM (Exp. 2). Combined injections of ondansetron (1.0 nmol/0.1 µl) and mCPP (0.03 nmol/0.1 µl) selectively blocked the anxiolytic-like effects of mCPP (Exp. 3). Neither ondansetron nor mCPP changed locomotor activity. The present results suggest that the anxiolytic-like effects exerted by 5-HT at 5-HT2C receptors may be modulated by 5-HT3 receptors located within the mouse PAG. FINANCIAL SUPPORT: UFSCar, CNPq

40. **Effects of chronic exposure to predator-associated stimuli on HPA-axis activation and anxiety-like behavior in mice**. Birkett, M.1; Redding, C.1, 2; Greene, T.1 1 Northern Arizona University, Flagstaff, AZ USA; 2 W.L. Gore & Associates, Flagstaff, AZ USA. Predator-associated stimuli are ethologically relevant stressors thought to model unconditioned and species-specific stress responses. Acute exposure to stimuli increases activation of the hypothalamic-pituitary-adrenal (HPA) axis and anxiety-like behavior in rodents. Chronic exposure may more fully model environmental stressors involved in symptoms of anxiety disorders, however protocols typically limit exposure to a brief period daily. To investigate the effects of continuous and chronic predator-associated stimuli

exposure on HPA-axis activation and anxiety-like behavior, adult, male C57 mice were singly housed for two weeks with no exposure to stimuli (control group, n=8), continuous exposure to fox urine (gauze with urine placed on top of cage lid, n=8), or continuous exposure to the presence of rats in the same housing room (n=32). In the rat presence condition, there was no physical interaction and mice were randomly assigned to cages with or without visual barriers and microisolator lids. There was no significant difference in HPA-axis activation or behavior among mice in different cage conditions, therefore data were combined for all subsequent analyses. Following two weeks of exposure, mice completed the open field test and blood was collected for corticosterone assay. Results revealed that rat stimuli exposure produced modest decreases in corticosterone concentration (p=.074) and increases in transitions into the open portion of the arena (p<.05), total distance traveled (p<.05) and time in center (p=.109) compared to fox urine exposure. Altogether, these results suggest that response to chronic and continuous exposure to predator-associated stimuli differs from acute exposure and may vary by stimuli type.

41. **Behavioral profile and hippocampal neurogenesis in an animal model of generalized anxiety disorder**. Dias, G.P.1,2,3; Bevilaqua, M.C.N.1,2,4; Silveira, A.C.D.L.1,2; Fleming, R.L.5; Carvalho, L.A.6; Cocks, G.3; Beckman, D.1,5; Hosken, L.C.1,2; Machado, W.S.1,2; Corrêa-e-Castro, A.C.1; Mousovich-Neto, F.7; Gomes, V.C.8,9; Bastos, G.N.T.10; Kubrusly, R.C.C.11; Corrêa da Costa, VM.7; Srivastava, D.P.3; Landeira-Fernandez, J.8, 12; Nardi, A.E.2; Thuret, S.3*; Gardino, P.F.1 1 Laboratory of Neurobiology of the Retina, Program of Neurobiology, Institute of Biophysics, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil. INNT Translational Neuroscience (CNPq), Brazil. 2 Translational Neurobiology Unit, Laboratory of Panic & Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil. INCT Translational Medicine (CNPq), Brazil. 3 Institute of Psychiatry, King's College London, United Kingdom. 4 Health and Environment School, Universidade Castelo Branco, Rio de Janeiro (RJ), Brazil. 5 Laboratory of Neurochemistry, Program of Neurobiology, Institute of Biophysics, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil. INNT Translational Neuroscience (CNPq), Brazil. 6 Laboratory of Comparative and Developmental Neurobiology, Institute of Biophysics, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil. 7 Laboratory of Endocrine Physiology, Program of Physiology and Biophysics, Institute of Biophysics, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro (RJ), Brazil. 8 Laboratory of Behavioral Neuroscience (LANEC), Department of Psychology, Pontifícia Universidade Católica do Rio de Janeiro (PUC-Rio), Brazil. 9 Department of Psychiatry and Neuroscience, Uniformed Services. University of the Health Sciences, Bethesda, MD, USA. 10 Laboratory of Neuroinflammation, Institute of Biological Science. Universidade Federal do Pará (UFPA), Rua Augusto Corrêa, 01 - 66075-110, Belém (PA), Brazil. 11 Laboratory of Neuropharmacology, Department of Physiology and Pharmacology, Biomedics Institute. Universidade Federal Fluminense, Rua Prof. Hernani Pires de Melo 101/213. São Domingos – Niterói (RJ), Brazil. 12 Laboratory of Comparative Psychology – Department of Psychology, Universidade Estácio de Sá (UNESA), Rio de Janeiro (RJ), Brasil. Anxiety is a complex psychobiological process which often emerges after experiences perceived as threatening. However, if the anxious responses are excessive or if they occur in the absence of stressors, it can give rise to a pathological condition, such as generalized anxiety disorder (GAD). The animal model for the study of GAD, the Carioca High Conditioned Freezing rats (CHF) present higher anxiety in the elevated plus maze and decreased social interaction. The aim of this work was to describe such aspects, presenting a new descriptive hypothesis for the neurobiological vulnerability to GAD. It has been observed that the CHF present: enhanced emotional memory (passive avoidance test: 64.94s±12.57 CT, n=18; 107.7s±7.096 CHF, n=19); unaltered spatial learning; higher levels of basal serum corticosterone (118.9ng/mL±27.97 CT; 339.0±49.38ng/mL CHF; n=10); reduced expression of glucocorticoid receptors in the dentate gyrus (3604±298.3 CT, n=12; 2385±266.5 CHF, n=9; CTCF); unaltered hippocampal volume; similar levels of proliferative cells in the dentate gyrus, decreased rates of neuronal differentiation (16310 cells / mm3±1630 CT, n=8; 11870 cells / mm3±1115 CHF, n=8); reduced number of tertiary dendrites (3.906±0.3147 CT, n=64; 2.703±0.2604 CHF, n=64), as well as reduced length (183.1µm±16.90 CT, n=64; 138.3µm±14.77 CHF, n=64), in the newly generated hippocampal neurons; increased number of dendritic spines in tertiary dendrites of dentate gyrus neurons (14.64±0.4105 CT, n=32; 17.10±0.5231 CHF, n=32; spines/10µm); increased expression of hippocampal BDNF (0.1731±0.05977 CT, n=4; 1.107±0.1659 CHF, n=4; optic density BDNF/α-tubuline); increased reuptake activity of aspartate in this brain structure (M=11300, DP=972.3, CT n=3; M=21870, DP=6567, CHF n=3), decreased GABA release (2.953±0.3489 N=6 CT;1.668±0.2151 N=5; ratio stimulated/basal release of [3H]-GABA). The CHF model present altered stress biomarkers, constituting an appropriate model for the study of anxiety, with a machinery for plasticity oriented for the facilitation of emotional memory retention.

42. **Reduced hippocampal volume in the Wistar-Kyoto rat as determined by high resolution anatomical MRI is associated with depressive and anxiety related behaviours.** Gormley S., 1,2, Kerskens, C.,1, Harkin, A.,1,2. 1. Trinity College Institute of Neuroscience, Trinity College, Dublin 2. 2. School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin 2. The inbred Wistar–Kyoto (WKY) rat is a putative animal model of depression and hyper-responsiveness to stress. We sought to investigate if WKY rats displayed anatomical volumetric abnormalities in cortical and limbic regions of the brain as measured by magnetic resonance imaging (MRI) when compared to the Wistar control strain. Male Wistar and WKY rats (200-250g n=10 per group) were subjected to a series of behavioural tests including exploratory behaviour in the open field (OF), behavioural despair in the forced

swim test (FST), anxiety-related behaviour in the elevated plus maze (EPM) and light/dark box and the object displacement task, a spatial memory task to test for hippocampal-dependent cognitive deficit. In preparation for MRI, the animals were anaesthetised using 5% isoflurane (maintained at 1.5%) and placed into a 7-Tesla MRI scanner (Bruker BioSpec 70/30 magnet system). Structural data was obtained via a high resolution anatomical scan (T2-weighted Rapid Acquisition with Relaxation Enhancement (RARE)) and analysed using automated voxel based morphometry (VBM) and manual tracing of regions of interest. The WKY strain was shown to exhibit a depressive and anxiety like phenotype across the range of behavioural paradigms including the FST, EPM, OF and light/dark box when compared to the Wistar control strain. The WKY strain exhibits volumetric abnormalities including a significant decrease in hippocampal volume and a significant increase in combined lateral and third ventricular volume when compared to the Wistar control strain. This observed decrease in hippocampal volume in the WKY rat correlates with performance deficit in the object displacement task. In conclusion reduced hippocampal volume in the WKY rat may provide a useful animal model to explore mechanisms underlying hippocampal volume changes of translational relevance to human depression and other stress related disorders.

43. **Effects of genetic background on visceral nociception, anxiety and depression-like behaviour: Responses of 12 mouse strains.** Moloney, R.D.1,2; Dinan, T.G.1,2; Cryan, J.F.1,3 1Laboratory of Neurogastroenterology, Alimentary Pharmabiotic Centre, Biosciences Institute, University College Cork, Ireland 2Department of Psychiatry, University College Cork, Ireland. 3Department of Anatomy and Neuroscience, University College Cork, Ireland. Introduction: Responses to painful stimuli differ between populations, ethnic groups, genders and even among individuals of a family. Furthermore, patients suffering from chronic pain disorders such as irritable bowel syndrome (IBS) also display co-morbid anxiety and depression. Previous studies in rodents have provided us with much needed data regarding strain differences using a vast array of somatic pain assays, but data regarding visceral nociception is still lacking. This study aimed to investigate strain differences in visceral nociception using manometric recordings of colorectal distension (CRD). Moreover, anxiety and depressive-like behaviours were also investigated. Methods: Adult male mice of the following inbred strains were used in this study: CBA/JHsd, C3H/HeNHsd, BALB/c OlaHsd, C57 BL/6JOlaHsd, DBA/2J RccHsd, CAST/EiJ, SM/J, A/J OlaHsd, 129P2/OlaHsd, FVB/NHan Hsd, and outbred strains: Hsd:ND4 (Swiss Webster), ICR (CD-1). CRD, open field and forced swim tests were performed to assess visceral sensitivity, anxiety and depressive-like behaviours respectively. Results: A significant effect of distension pressure was observed for all animals thus demonstrating that all animals respond to the CRD paradigm. We also found a significant effect of strain and a significant interaction of distension pressure X strain. Post hoc analysis revealed that CBA/JHsd and C3H/HeNHsd strains displayed a significantly greater response to CRD. Furthermore, these two strains travelled significantly less in the inner zone of the open field and display increased immobility in the forced swim test. Conclusion: This data demonstrates that strain differences occur in visceral nociception with both CBA/JHsd and C3H/HeNHsd strains displaying visceral hypersensitivity. Moreover, these two strains display anxiety and depressive-like behaviours, which are commonly co-morbid with chronic pain disorders. These findings reveal variations in basal nociception between mouse strains which may aid future work aimed at elucidating the mechanisms underlying visceral hypersensitivity in appropriate animal models.

44. **Chronic minocycline attenuates depressive-like behaviour and peripheral nerve injury-induced mechanical and cold allodynia in the olfactory bulbectomised rat**. Burke NN 1, Chen S 2, Finn DP 2, Roche M 1. 1 Physiology, 2 Pharmacology and Therapeutics, School of Medicine, NCBES Centre for Pain Research and Galway Neuroscience Centre, National University of Ireland Galway, Ireland. Altered glial function has been implicated in the pathogenesis of both chronic pain [1] and depression [2], two disorders which co-occur in up to 80% of patients [3]. However, the role of microglia in depression-pain co-morbidity has been under investigated. This study examined the effect of minocycline, a microglial inhibitor, on depressive-like behaviour and nociceptive responding in the olfactory bulbectomy (OB) model of depression, prior to and following peripheral nerve injury (L5/L6 Spinal Nerve Ligation (SNL)). Adult male Sprague Dawley rats were assigned to one of 4 groups: Sham-water, Sham-minocycline (80mg/kg in drinking water), OB-water or OB-minocycline, with water/minocycline treatment beginning 24hrs prior to sham/OB surgery and continuing throughout the experiment (n=10-11 per group). Locomotor activity (open-field) was assessed 2 weeks post-surgery and nociceptive responding to mechanical (von Frey) and cold (acetone-drop test) stimuli was examined prior to and following SNL. Data were analysed using ANOVA followed by Fisher's LSD post-hoc test. $P \leq 0.05$ was deemed significant. OB water-treated rats exhibited characteristic locomotor hyperactivity, which was attenuated by chronic minocycline treatment, indicative of an antidepressant-like effect. OB animals exhibited mechanical and cold allodynia, which was unaltered by chronic minocycline treatment. SNL resulted in mechanical and cold allodynia of the ipsilateral hind-paw of both sham and OB animals. SNL-induced cold, but not mechanical, allodynia was enhanced in OB rats when compared to sham-counterparts. Chronic minocycline prevented SNL-induced mechanical and cold allodynia in both sham and OB rats. In conclusion, inhibition of microglial activation elicits an antidepressant-like effect in the OB rat model, but does not alter associated allodynic responding to mechanical and cold stimuli. Minocycline prevented the development of mechanical and cold allodynia following peripheral nerve injury, in the presence and absence of a depressive-like phenotype. These data further supports a role for microglia in the pathogenesis of depression, the development of neuropathic pain, and the interaction between these disorders. Acknowledgements Research was

ethically approved by NUIG ACREC and financially supported by a College of MNHS postgraduate fellowship and Millennium fund, NUI Galway. The authors declare no conflict of interest

45. **Social behavioural deficits in a rat model of autism are associated with enhanced hippocampal N-acylethanolamine levels**. Kerr DM.1,2,3, Downey L.1, Conboy M.1, Finn DP.2,3 and Roche M.1,3 1Physiology and 2Pharmacology and Therapeutics, School of Medicine, 3NCBES Centre for Pain Research and Galway Neuroscience Centre, National University of Ireland, Galway, Ireland. The endocannabinoid system modulates emotionality and social behaviours, however it is unknown if alterations in this system occur in autism. The current study aimed to evaluate if alterations in the endocannabinoid system accompany behavioural changes in the valproic acid (VPA) rat model of autism. Pregnant female Sprague Dawley rats received VPA (600mg/kg s.c.) or saline on gestational day G12.5 and behavioural testing was carried out on the offspring during adolescence (PND33-40). Behaviours assessed included social investigatory behaviour (3-chamber sociability test), thermal nociception (hot plate test), anxiety-like behaviour (open field and elevated plus maze) and locomotor activity. Animals were sacrificed by decapitation either immediately following the sociability test or seventy-two hours following the final behavioural test, the brain removed and cortex, hippocampus and cerebellum dissected out, snap frozen and stored at -80oC. Concentrations of the endocannabinoids, anandamide and 2-arachidonylglycerol, and the N-acylethanolamines, N-oleoylethanolamine (OEA) and N-palmitoylethanolamine (PEA), were assessed using LC-MS/MS. Gene expression of endocannabinoid system receptors was determined using qRT-PCR. Data were analysed by unpaired t-test and $P<0.05$ was deemed significant. Prenatally exposed VPA rats exhibited reduced social investigatory behaviour, enhanced anxiety-related behaviour in the open field and thermal hyperalgesia, when compared to saline-treated counterparts. Immediately following the sociability test, anandamide, OEA and PEA levels were significantly increased in the hippocampus, but not cortex or cerebellum, of VPA-exposed rats, effects not observed seventy-two hours after the final behavioural test. Although CB1 and CB2 receptor expression were not altered, VPA-exposed rats exhibited reduced PPARα and GPR55 expression in the cortex and PPARγ and GPR55 expression in the hippocampus, further receptor targets of the endocananbinoids. These data indicate that alterations in the endocannabinoid system may underlie some of the behavioural changes such as social impairments observed in autism spectrum disorders. Acknowledgements: This work was funded by the NUI Galway Millennium Fund and disciplines of Physiology and Pharmacology and Therapeutics, NUI Galway, Ireland

46. **Involvement of different subnuclei of the dorsal raphe nucleus in the panicolytic-like effect caused by prelimbic cortex activation in rats.** Zangrossi, H; Spiacci, A. Yamashita, PSM. School of Medicine of Ribeirao Preto, University of Sao Paulo, Brazil. The dorsal raphe nucleus (DRN), the main source of 5-HT projections to limbic areas involved in the regulation/genesis of anxiety and fear, is densely innervated by the medial prefrontal cortex (MPFC). Glutamatergic projections linking the MPFC to the DRN are shown to either indirectly inhibit 5-HT cell firing, via activation of local GABAergic interneurons, or to directly excite these cells. In the present study, we investigated the effect of intra-prelimbic cortex (PL) injection of the GABAA receptor antagonist picrotoxin on anxiety- (i.e. inhibitory avoidance) and panic- (i.e. escape) related defensive behaviors generated by the elevated T-maze (ETM). Intra-PL injection of picrotoxin (0.08, 0.16, 0.32 nmol) in male Wistar rats impaired escape expression, indicating a panicolytic-like effect, without interfering with inhibitory avoidance acquisition. This selective anti-escape effect was accompanied by an increase in the number of doubly-immunostained cells for Fos protein and tryptophan hydroxylase in the middle and caudal level of the DRN, specifically within the sub-regions dorsal, caudal and lateral wings of the DRN. The results suggest that the activation of these subnuclei may lead to 5-HT release in the dorsal periaqueductal gray matter, which ultimately causes a panicolytic-like effect in the ETM. Financial support: FAEPA and CNPq (Brazil).

47. **Ghrelin regulates anxiety-like behavior in mice potentially through hypothalamic-purity-adrenal axis interaction.** van Oeffelen, W.E.P.A.1; Clarijs, A.W.H.C.2,5;Dinan, T.G.2, 3;Cryan, J.F.1, 2 1Department of Anatomy & Neuroscience, 2 Food for Health, Ireland, 3Alimentary Pharmabiotic Center, 4Department of Psychiatry, University College Cork, College Road, Cork, Ireland, 5Avans University of Applied Science, Breda, The Netherlands. Ghrelin is a peptide that is well known for its hunger-stimulation after binding to the growth hormone secretagogue receptor 1α (GHSR1α) in the hypothalamus. Additionally, ghrelin plays a role in anxiety and depression. In this context, we showed that GHSR1α dimerises with other brain-receptors involved in anxiety and depression (Schellekens H. et al. 2012). Another mechanism by which GHSR1α may impact mood is via interactions with the hypothalamic-pituitary-adrenal (HPA)-axis, the main pathway which regulates the body's response to stress. As such, we investigated whether ghrelin can regulate the HPA-axis. Two cohorts of male C57BL6/j mice were calorie restricted to stimulate ghrelin secretion and examined for anxiety and depressive symptoms. Calorie restriction induced hypertrophy of the adrenal glands, suggesting an HPA-axis mediated reaction to stress. A trend towards significantly reduced anxiety-like behaviour was observed in the elevated plus maze, with no effect in depressive-like behaviour in the forced swim test. To further evaluate the role that ghrelin plays in the regulation of mood, we developed a lentiviral gene-transfer vector which expresses a green fluorescent protein. This vector will serve as the backbone construct for knockdown and overexpression of GHSR1α in the hypothalamus. In conclusion, calorie restriction reduces anxiety-like behaviour in mice potentially via a ghrelin-

HPA axis interaction. As such, future studies using this model in conjunction with the viral construct will allow the assessment of ghrelin in the regulation of mood.

48. **Processing emotional stimuli in older adults: Faces come first**. Belham, F.; Satler, C.; Carvalho, C.; Garcia, A.; Tomaz, C. University of Brasilia, Brasília, DF Brazil. Cognitive processes, such as memory, are influenced by emotional processing, indicating a profound interaction of these domains across lifespan. The aim of this study was to investigate if age-related differences are the same when the stimuli to be remembered have distinct characteristics. Is the performance of older adults more influenced when the emotional information is presented in context pictures or in facial expressions? Performances of 64 older adults (OA: 31M; age 70,45±6,55) and 84 younger adults (YA: 39M; age 21,23±2,63) were compared in a spatial-delayed recognition span task, in which the subject had to identify the new location of one stimulus in a crescent set of identical stimuli (until 8) presented in a screen. Emotional and non-emotional pictures about context information (from the IAPS) and facial information were used as stimuli. Results showed that OA performed slower and more poorly than YA across all types of stimuli. YA were faster when responding to context pictures than to facial pictures ($p<0.001$); however the number of right answers was statistically the same. OA showed the opposite pattern, responding faster and more accurate to faces than to context information ($p<0.001$). These results are according to previous studies suggesting that cognitive aging brings differences in the emotion processing ability; probably due to deficits in the efficient cognitive resources available to perform a cognitive task. In addition, it seems that facial stimuli attracted more effectively these available resources, particularly attention, increasing performance. On the other hand, IAPS pictures present contextual information that depicts diverse semantic content, which could interfere with the processing of emotional information in OA and, therefore, could be associated with low performance on the task.

49. **Comparison of two different protocols of chronic social defeat in adolescent C57BL/6 male mice on anxiety and depression-related behaviors**. Chiavegatto, S.; Amaral, C.E.; Soares, R.B.; Rodrigues, A.C.D.; Reigado, C.N.; Resende, L.S.; Alves-dos-Santos, L. Dept of Pharmacology, Biomedical Sciences Inst., University of Sao Paulo, SP, and National Inst. for Developmental Psychiatry (INPD-INCT), Brazil. We investigated the effects of two different protocols of prolonged social defeat over adolescence on anxiety- and depression-related behaviors. Male C57BL/6 mice at 30-days of age were exposed to a previously selected CD-1 aggressive male mouse in the following ways: 1) Once daily, for 21 days in a 30-min session; encounters were performed in the home cage of an aggressor, and after the first bout of attack a wire mesh was introduced in the center of the home cage to physically separate both mice until the end of the session; the defeated mouse was then returned to its cage. 2) Once daily, for 10 days in a 5-min session; encounters were in the home cage of an aggressor and after the session the defeated mouse was left isolated for 24h in an adjacent compartment separated from the aggressor´s cage by a perforated acrylic partition. Appropriate controls for both protocols were exposed to same situations without the aggressor. We did several sets of experiments (8-12 mice/each) for both protocols. Behavioral tests included EPM and sucrose preference (SP = anhedonia). Defeated mice from protocol 1 showed reduced SP and anxiety-related behaviors, when compared to controls ($p<0.05$) in most, but not all sets. Defeated mice from protocol 2 showed both anhedonia and anxiety behaviors ($p<0.05$) in all sets, with lower variability between animals when compared to the protocol 1. Our results show that prolonged social defeat occurring during adolescence in male mice induces behavioral alterations indicative of anxiety and depression states, similarly as previously shown for adult mice. Although we observed high behavioral variability in defeated mice using both protocols, fewer days with prolonged physical defeat sessions associated with extended sensory contact with the aggressor were more effective to model these behavioral consequences of psychosocial stress in adolescents. Financial Support: CNPq-INCT and CAPES, Brazil.

50. **Adverse social environment in early life that has selective long-lasting effects on social interaction and plasma oxytocin of adult rats**. Henriques, T.P. 1; Diehl, L.A. 2; Corrêa, C.N. 1; Pardo, G.E. 1; Souza, M.A. 1; Caceres, R.C. 1; Winter, A. 1; de Almeida, R.M.M. 3; Dalmaz, C. 2; Lucion, A.B. 1 1Physiology, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil; 2Biochemistry, Federal University of Rio Grande do Sul; 3Institute of Psychology, Federal University of Rio Grande do Sul. The first 2 weeks of life in rats is a neurodevelopmental sensitive period when pups are susceptible to environmental events, such as maternal care and stress. Early events may have long-lasting effects on animal's behavior and neuroendocrinology. We investigated the effects of the Social Instigation (SI) as a neonatal intervention upon anxiety, stress responses and social interaction in adulthood. At postpartum days 2 and 5 (P2 and P5), Wistar dams were submitted to the SI paradigm: an adult male inside a perforated tube was placed in the dam's cage with its pups for 5 min. After a 5 min interval, another male was introduced into the home-cage for 10min. The control group (C) was left undisturbed. At P90, C and SI male and female offspring were studied. The social interaction apparatus consisted of 2 boxes (A and B) connected to a third (neutral). One rat was placed into each box (A and B). Each rat remained isolated for 24 h. The doors were opened allowing both rats the exploration of all 3 boxes for 15 min. Other rats were tested on plus maze task (PM) for 5 min. A third group was submitted to a restraint stress (RS) for 30 min and had their plasma hormones analysed by ELISA. In the social interaction test, SI and male rats showed the higher lateral attack frequencies. No differences between C and SI rats were found in PM. On RS, plasma corticosterone was increased in all stressed rats compared to the non-stressed ones. Plasma oxytocin was decreased in SI compared to C rats,

without effect of RS. There were no effects on arginine-vasopressine levels. Minor sex effects were found. Neonatal interventions usually lead to a variety of long-lasting behavioral and neuroendocrine alterations. However, the SI caused no effects on anxiety and stress responses of the adult rats. Interestingly, SI specifically led to increased aggressivity and decreased plasma oxytocin levels in adulthood.

51. **Contextual Fear Conditioning in Maternal Separated Rats: The Amygdala as a site for alterations**. Diehl, L.A.1; Laureano, D.P.1; Benitz, A.N.D.1; Noschang, C.1; Ferreira, A.G.K.1; Scherer, E.B.1; Machado, F.R.1; Henriques, T.P.2; Wyse, A.T.S.1; Molina, V.3; Dalmaz, C.1 1Departamento de Bioquímica, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; 2Departamento de Fisiologia, Universidade Federal do Rio Grande do Sul; 3Departamento de Farmacología, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Córdoba, Argentina. The first two weeks of life are a critical period for neural development in rats. Repeated long separations from the dam are considered one of the most potent stressors to which rat pups can be exposed. Prolonged periods of maternal separation (MS) permanently modifies neurobiological and behavioral parameters. The aim of this study was to verify the effects of maternal separation during the neonatal period on memory as well as on biochemical parameters (Na+, K+-ATPase and antioxidant enzymes activities) in the amygdala of adult rats. Females and male Wistar rats were subjected to repeated maternal separation (incubator at 32°C, 3h/day) during postnatal days 1-10. At 60 days of age, the subjects were exposed to a Contextual fear conditioning task. One week after the behavioral task, animals were sacrificed and the amygdala was dissected for evaluation of Na+, K+ -ATPase and antioxidant enzymes activities. Student-t test showed significative MS effect, causing an increase of freezing time in the 3 exposures to the aversive context in both sexes. Considering biochemical parameters Student-t test showed significative MS effect causing an increase of Na+, K+ ATPase activity in both sexes. On the other hand, no differences were found among the groups on the antioxidant enzymes activities (SOD, GPx, CAT) in male rats, but in females, we found a significative MS effect, causing an increase of CAT activity and no differences were found among the groups on SOD and GPx activities. Our results suggest a role of early rearing environment in programming fear learning and memory in adulthood. An early stress experience such as maternal separation may increase activity in the amygdala (as pointed by the increased activity of Na+,K+-ATPase), affecting behaviors related to fear in adulthood, and this effect could be task-specific.

52. **Increased social anxiety and alteration of serotonergic gene expression after priming of CRF receptors in the bed nucleus of the stria terminalis.** Donner, N.C.[1]; Mani, S.[1]; Johnson, P.L.[2]; Fitz, S.D.[2]; Shekhar, A.[2]; Lowry, C.A.[1] [1]University of Colorado Boulder, Boulder, Colorado USA; [2]Indiana University School of Medicine, Indianapolis, Indiana USA. We previously demonstrated that repeated stimulation of corticotropin-releasing factor (CRF) receptors within the basolateral amygdala (BL), which leads to a chronic anxiety state and panic-like responses following intravenous infusion of sodium lactate, alters the expression of *tph2*, the gene encoding the rate-limiting enzyme for brain serotonin synthesis (tryptophan hydroxylase 2) specifically within the "lateral wings" of the serotonergic dorsal raphe nucleus (DR). These effects may be due to disruption of serotonergic control of panic-like anxiety states via CRF-mediated signaling from central amygdala (CE)-originating projections to the DR. In contrast, CRF signaling from the bed nucleus of the stria terminalis (BNST) to the DR may promote conflict anxiety-like emotional states without affecting vulnerability to panic-like responses to sodium lactate. We here primed adult, male rats for five consecutive days with bilateral, subthreshold injections of urocortin 1 (UCN1, 6 fmoles/100 nl per side, n=11) or vehicle (n=11) into the BNST, evaluated the rats' anxiety in the social interaction (SI) test one day prior to the start of priming and two days after the final intra-BNST injection, and performed *in situ* hybridization histochemistry for *slc6a4* (encoding the serotonin transporter, SERT) and *tph2* mRNA on hindbrain sections measured 3 days after the termination of priming. BNST priming with UCN1 reduced SI behavior, an index of increased conflict anxiety, and elevated *slc6a4* expression within the rostral part of the median raphe nucleus (MnR) without altering *slc6a4* expression in the DR. Altered *slc6a4* expression in the MnR may thus be of relevance for the manifestation of social conflict anxiety and clinical depression. We are currently analyzing *tph2* mRNA expression as well. Our research was supported by NIMH grant # MH65702.

53. **Not presented.**

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54. **Not presented.**

55. **Not presented.**

56. **Schizophrenia-like abnormalities in mice due to adolescent exposure to Toxoplasma gondii**. Geetha Kannan1, Ye Li2, J-C Xiao2, Emily G. Severance2, Lorraine Jones-Brando2, Robert H. Yolken2, and Mikhail V. Pletnikov1 1 Division of Neurobiology; Department of Psychiatry; Johns Hopkins University; Baltimore, MD; USA 2 Stanley Division of Developmental Neurovirology; Johns Hopkins University; Baltimore, MD; USA. Toxoplasma gondii (T. gondii) is an etiological factor implicated in schizophrenia. Insults during neurodevelopment have also been associated with disease. Using mouse models, we sought to determine the contribution of the timing of T. gondii infection in the development of schizophrenia endophenotypes. To do so, we evaluated the effects of infection with the T. gondii strain Prugniaud (PRU) during either adolescence or adulthood on male Balb/C mouse behaviour. In addition, we looked at changes in molecular correlates implicated in schizophrenia-like behaviour in mice infected during adolescence. As compared to controls, infection with PRU during adolescence led to hyperactivity and greater MK-801-induced impairment of pre-pulse inhibition of the acoustic startle. These changes were not seen in mice infected during adulthood. We also found decreased expression of NMDAR-1 and SNAP25 and increased levels of C1q in the hippocampus but not frontal cortex of mice infected during adolescence. Our findings suggest that adolescent exposure to T. gondii is important in contributing to the development of schizophrenia.

57. **The microbiome-gut-brain axis regulates the survival of newly-born cells in the adult hippocampus.** Ogbonnaya, S.1, 3; Cryan, J. F.1, 2; O'Leary, O.F.1 1Department of Anatomy, and Neuroscience, University College Cork, Cork, Ireland. 2Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland. 3Department of Neurosurgery, Cork University Hospital, Cork, Ireland.. Germ-free (GF) mice exhibit alterations

in the corticosterone response to stress, anxiety, and hippocampal serotonin (5-HT) & brain-derived neurotrophic factor (BDNF) concentrations. Corticosterone, BDNF, and 5-HT are important regulators of adult hippocampal neurogenesis, which in turn plays a functional role in learning & memory, anxiety and the stress response. Exactly how adult neurogenesis plays a role in diverse functions such as learning & memory and the stress response is currently unknown but accumulating evidence suggests that the hippocampus is functionally segregated into dorsal (dHi) and ventral (vHi) regions and that this might also apply to neurogenesis within the hippocampus. Specifically, the dHi appears to play a preferential role in spatial learning & memory while the vHi plays a preferential role in anxiety & the stress response; processes which also involve hippocampal neurogenesis. Since GF mice exhibit altered concentrations of substrates that affect neurogenesis, it is plausible that adult hippocampal neurogenesis might also be altered in these mice. The aim of this study was to determine whether the proliferation and survival of newly-born cells along the dorso-ventral axis of the adult hippocampus is altered in GF mice compared to conventionally colonised (CC) mice. Compared with CC mice, GF mice exhibited increased survival of newly-born cells in the dHi ($p=0.008$), and these effects were not reversed by bacterial colonisation post weaning. This suggests that the gut microbiome can influence the survival of newly-born cells in the hippocampus, and that there is a critical period during development when this occurs. Whether these cells differentiate into neurons is currently being investigated. The specific effect in the dHi raises the possibility that GF might exhibit altered spatial memory.

Thursday, June 27

8:30-10:30 **Symposium: Animal models of autism: Assessing genetic vulnerability, environmental risk factors, and new strategies for intervention. Chair: Tomasz Schneider.** *Guttenberg Suite*

8:30 **Mouse models of autism phenotypes as preclinical screens for drug discovery.** Authors: Sheryl S. Moy, Brian L. Teng, Randal J. Nonneman, Kara L. Agster, Viktoriya D. Nikolova, Tamara T. Davis, Natallia V. Riddick, Lorinda K. Baker, Cort A. Pedersen, and Michael B. Jarstfer Affiliations: Carolina Institute for Developmental Disabilities, Department of Psychiatry, and UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA. The autism spectrum disorders (ASDs) are a heterogeneous group of childhood conditions that share specific core features, including impaired social interaction and abnormal repetitive behavior. There are currently no pharmaceutical agents for treatment of core ASD symptoms, although risperidone, an antipsychotic drug, has been approved for use against comorbid irritability in autistic children and adolescents. However, emerging evidence from clinical studies suggests that oxytocin could have therapeutic efficacy for social deficits and other ASD symptoms. Significant drawbacks to the use of oxytocin itself in treatment regimens include a markedly short plasma half-life and poor ability to penetrate the blood-brain barrier. Our research group has been investigating mouse models of ASD-like behavior as preclinical screens for the development of more bioavailable oxytocinergic compounds. We have found that oxytocin has significant prosocial effects in two inbred mouse strains, BALB/cByJ and C58/J, following subchronic, but not acute, treatment regimens. Further, acute oxytocin decreased abnormal repetitive behavior in C58/J and did not induce hypoactivity or anxiolytic-like effects in an open field test. These findings provide validation of the BALB/cByJ and C58/J models as useful platforms for screening novel drugs for intervention in ASDs. This work was supported by the US Department of Defense (AR1002312), NIH-NICHD (P30 HD03110), and Autism Speaks.

9:00 **Animal model of autism induced by prenatal exposure to valproic acid.** Tomasz Schneider, Experimental Psychology, University of Oxford, South Parks Road, Oxford UK, OX1 3UD tomasz.schneider@psy.ox.ac.uk. In this presentation, I will focus on one of the best validated animal models of autism induced by prenatal exposure to valproic acid (VPA) during early gestation. VPA rodents show several brainstem and cerebellar abnormalities resembling those found in autistic patients and a plethora of behavioural aberrations including decreased social interactions, increased repetitive behaviours, higher anxiety, hyperactivity, sensory aberrations, impaired pre-pulse inhibition, and faster acquisition of eye-blink conditioning. Interestingly, behavioural aberrations described in VPA rats are observed mostly in males and can be reversed by environmental enrichment procedure. These might resemble both disproportion in boys to girls ratio in autism and efficacy of early behavioural-cognitive intervention in some patients with autism. VPA rats express also molecular and immunological aberrations resembling those observed in autism, e.g., increased serotonin level in several brain structures and hyperserotoninemia, increased frontal cortex dopamine level, enhanced excitatory transmission, and decreased cellular immune response. Similarities in behavioural, anatomical, biochemical and immunological pathology in autism and VPA rats suggest the utility of the VPA rodent model of autism for defining common pathways for dysregulation of normal developmental patterns and assessing the time course and sources of vulnerability to that still incurable disorder. I will show recent empirical and theoretical applications of VPA model towards better understanding and potential new treatments for autism.

9:30 **Autism spectrum disorders, epigenetics and histone deacetylase inhibitors.** Regan C, University College Dublin, Dublin, IRELAND. The dynamic modification of chromatin complexes by the addition of acetyl groups to core histone proteins by histone acetyltransferases (HATs) and their removal by histone deacetylases (HDACs) provides a mechanism by which genetic and environmental factors may induce phenotypic change over an extended period of time. This has led to the suggestion that altered epigenetic patterning may contribute to the pathophysiology of psychiatric

disorders that emerge during development, including autism spectrum disorder (ASD). This developmental disorder arises in approximately 1% of the world-wide population and is comprised of a heterogenous group of conditions characterised by impairments in reciprocal social interactions and the presence of restricted and repetitive and stereotyped behaviours. Although highly heritable, the aetiology of ASD is largely unknown and only 5-15% of cases have an identifiable aetiology. Rett's syndrome, for example, relates to loss of function of the methyl CpG binding protein 2 (MECP2) that regulates transcriptional repression through its interaction with methylated DNA and HDAC1 and HDAC2. Epidemiological studies have demonstrated teratogen exposure during the first trimester to be significantly correlated with an increased risk of developing ASD and this has been associated with abnormal synapse remodelling arising from dysregulation of synaptic development proteins, including cell adhesion molecule function and glycosylation state. We were interested, therefore, to determine the extent to which such an environmental risk factor might provide face and construct validity. We used adult rats of dams which receive a single dose of the valproic acid (VPA) teratogen at time of neural tube closure. Using this VPA rat model of ASD, we focussed on cognition as social reciprocation deficits are a major core symptom of ASD. We also attempted to provide some understanding on the nature of this cognitive phenotype by employing a biological motion paradigm as this has a significant correlation with IQ in human ASD. A spatial learning paradigm was employed to account for the consequences of the structural deficits observed in the hippocampus of patients with ASD as these may contribute to the dorsal stream processing deficits associated with this condition. As a measure of construct validity, we evaluated cell adhesion molecule function, specifically neural cell adhesion molecule (NCAM) polysialylation (PSA) state, as this has previously been implicated in the pathogenesis of ASD. Finally, given the premise that ASDs are linked to epigenetic patterning and that covalent modification of core histone proteins has been demonstrated to underpin behavioural modification and synaptic plasticity in adult rodents, we determined the impact of HDAC inhibition on the cognitive and cellular deficits induced by in utero exposure to VPA in order to provide confidence in the predictive validity of this model. This work was funded and performed by Berand Neuropharmacology.

10:00 **Autism spectrum disorders and the primate brain.** Watson, K. 1, Platt, M. 1 1. Duke University, Durham, North Carolina, USA. Autism spectrum disorders (ASDs) are marked by dysfunctional social behavior and cognition, and a greater understanding of the biological substrates of typical social behavior in animal models will further our understanding of the etiology of ASDs. Non-human primates (NHPs) provide an attractive model for ASDs, due in part to the complexity and dynamics of social structures, reliance on vision for social signaling, and deep homology in brain circuitry mediating social behavior and reward. Primate behavior and ecology, as well as the neurobiology of the primate brain, have been studied for decades, and these bodies of knowledge may be leveraged to understand the neurobiological basis of primate social behavior. By harnessing the behavioral similarities in human and non-human primates (NHPs), we developed laboratory tasks that are both ethologically relevant to monkeys as well as to behavioral disruptions induced by ASD. Use of these tasks have revealed the ways in which individual neurons in the primate frontal lobe represent social information, the role of oxytocin in mediating social attention and reward, and the relationships between genetic polymorphisms and social behavior. These findings shed light on the mechanisms underlying primate social behavior and, consequently, a basis from which to explore the etiology of ASDs. We argue that NHPs are an under-used animal model whose expanded use in autism research would help bridge the gap between the more widely used human and mouse-model-based approaches.

8:30-10:30 **Symposium: Female vulnerability to depression: From molecules to behavior.** Chairs: **Debra Bangasser; Christina Dalla.** *Tara Suite*

8:30 **Animal models of depression: How about females?** Christina Dalla, Dep. of Pharmacology, Medical School, University of Athens, Greece. Women are more prone to mood disorders than men and the underlying mechanisms are not fully understood. During the last decade, our group has studied sex differences in behavior, as well as in neurochemical, neurobiological and neuroplasticity indices in different models of depression, such as the forced swim test (FST), the chronic mild stress (CMS) and others. CMS causes alterations in the estrous cycle, decreased serotonergic activity in the hippocampus of female rats, as well as enhanced 5-HT1A mRNA in the hippocampus of males only. In the FST, serotonergic turnover ratio is also decreased in female rats and this is accompanied by decreased hypothalamic 5-HT1A receptor mRNA. At a behavioural level, depression-like symptomatology in the FST is more evident in females than males, whereas this does not depend on sex differences in circulating corticosterone levels. On the other hand, swimming duration during FST, which is indicative of serotonergic activity, is lower when estrogens are low and correlates positively with the estrogen-dependent uterus weight. Further studies during the estrous cycle with the SSRI antidepressant sertraline revealed that in FST, it is preferable to use female rats during the late estrous – diestrous I phases (low/stable estrogens and progesterone), in order to access antidepressant activity. Finally, lesion and inactivation studies showed that the integrity of the circuit hippocampus – prefrontal cortex is necessary for the expression of passive (depressive) behaviors in the FST in both sexes. However, when this circuit is disrupted sertraline lacks an antidepressant effect only in males. This latter finding can be attributed to sex differences in basal levels of FST behavior. Overall, our data point to sex-differentiated neurobiological and behavioural indices in all animal models of depression. These differences need to be recognized, in order to use animal models effectively in the investigation of mood disorders and their treatment in men and women.

9:00 **Sex differences in stress-related psychiatric disease: Novel mechanisms for interactions between stress and arousal systems.** Debra A. Bangasser, Ph.D.1, Hua Ding, Ph.D.2, Steven Seeholzer, Ph.D.2, and Rita J. Valentino2 1Temple University, Philadelphia, PA, USA 2The Children's Hospital of Philadelphia, Philadelphia, PA, USA. Women are twice as likely as men to suffer from depression. Depression involves dysregulation of stress and arousal systems, so sex differences in these systems may explain this disparity. Previously, we found that noradrenergic neurons in the locus coeruleus (LC) arousal system of female rats were more sensitive to the stress neuropeptide corticotropin releasing (CRF) than neurons of males. These electrophysiological findings were linked to increased CRF receptor (CRFr) coupling to the Gs protein in females. Additionally, following stress the CRFr internalizes in males but not females, an effect associated with increased βarrestin binding in males. Activation of βarrestin also initiates its own suite of signaling cascades. Thus, the CRFr in males may be biased towards βarrestin signaling and away from Gs signaling, while in females the pattern may be opposite. To test this, we conducted a phosphoproteomic analysis comparing cortical tissue of male and female CRF overexpressing mice because these mice have increased CRFr activation. Roughly 15% of the phosphoproteins were sexually distinct and these were overrepresented in different signaling pathways. βarrestin initiates small GTPase signaling and GTPase signaling was prevalent in males. Gs activation leads to protein kinase A (PKA) signaling and this pathway was overrepresented in females. Moreover, PKA mediates LC neuronal responses to CRF to a greater degree in females than males, so the signaling changes in cortex mirror physiological finding in LC neurons. Together these studies suggest that sex differences in CRFr signaling render female LC neurons more sensitive to CRF. As LC neuronal firing is correlated with arousal, conditions of excessive CRF release would shift females more easily into the dysregulated state of hyperarousal that is characteristic of depression. NIH grants MH040008 & MH092438.

9:30 **Epigenetic regulation of sex differences in the behavioral response to stress.** G.E. Hodes, M. Pfau, H.F. Ahn, X. Liu, D.J. Christoffel, S.A. Golden, M. Heshmati, J. Feng, L. Shen E.J. Nestler and S.J. Russo. Fishberg Department of Neuroscience and Freidman Brain Institute, Icahn School of Medicine at Mt. Sinai. New York, NY. To elucidate the genetic and epigenetic mechanisms that contribute to sex differences in the stress response, we exposed mice to a 6-day variable stressor that resulted in depression and anxiety associated behaviors only in females. Patterns of gene expression varied greatly between males and females in the nucleus accumbens (NAc) a brain region involved with reward processing implicated in mood disorders. Many more genes were regulated in males compared to females suggesting that resiliency to stress in males is an active process. Investigation of a class of enzymes, DNA methyltransferases (Dnmts), indicated that males and females had different baseline and stress-induced patterns of transcriptional regulation. We used a combination of viral-mediated gene transfer and conditional knockouts to achieve NAc specific adult regulation of Dnmt 3a and examined its functional relevance to depression and anxiety-associated behaviors. Overexpression of Dnmt 3a in NAc was sufficient to induce depression-associated behaviors in males. Removal of Dnmt 3a from the NAc of females was antidepressant and blocked the behavioral effects of the 6-day variable stress. Dnmt 3a functionally contributes to an individual's vulnerability or resilience to stress suggesting that regulators of de novo DNA methylation in the adult brain may be novel mechanisms and potential drug targets for personalized treatment of mood disorders. NIMH: 1R01MH090264, NIDA: 5TDA07135-28, NIMH: P50MH096890. NARSAD Young Investigator Award.

10:00 **Structural Plasticity and Cognitive Function: Resilience and Vulnerability During the Postpartum Period.** Benedetta Leuner, The Ohio State University, Columbus, OH, USA. Numerous neuroendocrine, neuronal, and behavioral adaptions occur during pregnancy and the postpartum period that enable females to cope with the challenges of motherhood. This talk will discuss how caregiving and the accompanying experiential and hormonal changes positively influence the prefrontal cortex, a brain region involved in cognition, mood regulation, and maternal care. Specifically, I will describe data showing that the postpartum period is associated with the promotion of neuronal growth in the prefrontal cortex and enhanced cognitive function. I will also discuss the negative impact of pregnancy stress, a risk factor for postpartum depression, on these structural and functional alterations as well as its adverse effects on maternal and affective behaviors. A better understanding of maternal brain plasticity, and conditions which compromise this plasticity, may provide mechanistic insights into enhanced vulnerability to mental illness during the postpartum period.

10:30-11:00 **Coffee/Tea Break**. *Tara Suite*

11:00-12:00 **Bench-to-Bedside Lecture: Phil Skolnick, Ph.D., D.Sc. (hon.), National Institute on Drug Abuse. Developing drugs to treat substance use disorders (SUDS): Why haven't we been more successful?** *Tara Suite*

Developing drugs to treat substance use disorders (SUDS): Why haven't we been more successful? Phil Skolnick, Division of Pharmacotherapies & Medical Consequences of Drug Abuse, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD USA. The goal of developing highly effective medications to treat substance use disorders (SUDs) remains largely unmet. While there are multiple, albeit imperfect options to treat opiate and tobacco use disorders, there are no approved medications to treat cocaine, methamphetamine, and cannabis use disorders. The root cause of this dearth of effective/approved medications is a general lack of interest (i.e., investment) by the pharmaceutical/biotechnology sectors. Among the explanations for the indifference are: a) a perceived small market size;

b) a high regulatory bar for approval of medications; c) difficulties in executing a clinical development program in patients that often have serious co-morbidities. Despite these obstacles, the next decade may yet be transformative for the treatment of SUDs. Thus, advances in the neuroscience of addiction have revealed multiple targets (e.g., mGluR2 and serotonin2c receptors) for potential therapeutic intervention. Compounds targeting these receptors are in various stages of development for other indications, and may become available for clinical evaluation in SUDs. In parallel, there has been remarkable progress in the development of biologics, including vaccines and genetically modified enzymes, capable of targeting specific drugs of abuse. In this presentation, I will discuss the obstacles and opportunities associated with developing drugs to treat SUDs, highlighting several promising therapeutic approaches on the near-to-mid term horizon.

12:00-1:30 **Break**

1:30-3:30 **Oral Session 1: TBI, psychosis, and depression. Chair: Stephen Kent.** *Tara Suite*

1:30 **Administration of nimodipine during the sensitive period for brain sexual-differentiation leads to sex-specific behavioral effects in adulthood: Neurodevelopmental implications for depression**. Michal Arad1, Margaret M. McCarthy1,2,3,4, Todd D. Gould1,2,4,5 1 Department of Psychiatry, 2 Program in Neuroscience, 3 Departments of Physiology, 4 Department of Pharmacology, 5 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 diagnosis of bipolar disorder and depression. CACNA1C codes for Cav1.2, which is an L-type voltage-gated calcium channel α1 subunit. Recently, we reported that Cacna1c haploinsufficiency in the mouse alters depression- and anxiety-like behaviors in a sex-dependent manner. Given that male and female haploinsufficient mice share reduced levels of Cav1.2, but differ in their behavior, our aim was to assess whether a blockade of Cav1.2 during a sensitive period for sexual differentiation of the brain will lead to a similar sex-specific behavioral pattern. To that end, male and female C57BL/6J mice received bilateral intracerebroventricular (0.25µl/side) injection of vehicle, 0.025µg/0.25µl or 0.25µg/0.25µl of nimodipine (Cav1.2 blocker) on postnatal day (PND) 0. A forth group of male and female mouse pups did not receive any injection. At adulthood (>PND77), all mice were tested in behavioral procedures that assess depression- and anxiety-related behaviors, cognitive performance, and spontaneous or amphetamine-induced locomotor activity. Neonatal administration of nimodipine did not affect cognitive performance (Y-maze), locomotor activity (Open Field; OF), or anxiety-related behavior (Elevated Plus Maze, OF) in adults. Depressive-like behavior (Forced Swim Test, Learned Helplessness) was modulated in a sex- and dose-dependent manner: in females the low dose increased while the high dose decreased depression-like behavior, whereas no effect was observed in the males. Increased locomotion in response to amphetamine was observed only in females treated with the low dose of nimodipine. These findings provide further support for the sex-dependent role of L-type calcium channels in the development of depression, suggesting that neonatal changes in activity of L-type calcium channels alters 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 mechanism underlying sex-specific risk for mood disorders.

1:42 **Transcranial infrared laser stimulation of human cognitive and emotional functions**. Francisco Gonzalez-Lima* and Douglas W. Barrett, Department of Psychology and Institute for Neuroscience, University of Texas at Austin, Austin, TX 78712. This talk describes the first controlled study demonstrating the beneficial effects of transcranial laser stimulation on cognitive and emotional functions in humans. Photobiomodulation with red to near-infrared light is a novel intervention shown to regulate neuronal function in cell cultures, animal models, and clinical conditions. Light that intersects with the absorption spectrum of cytochrome oxidase was applied to the forehead using the laser diode CG-5000, which maximizes tissue penetration and has been used in humans for other indications. We tested whether low-level laser stimulation produces beneficial effects on frontal cortex measures of attention, memory and mood. Reaction time in a sustained-attention psychomotor vigilance task was significantly improved in the treated (n = 20) vs. placebo (n = 20) groups, especially in high novelty-seeking subjects. Performance in a delayed match-to-sample memory task showed also a significant improvement in treated vs. control groups as measured by memory retrieval latency and number of correct trials. The Positive and Negative Affect Schedule, which tracks self-reported positive and negative affective (emotional) states over time, was administered immediately before treatment and two weeks after treatment. The results showed that overall affect improved significantly in the treated group due to more sustained positive emotional states. These data imply that transcranial laser stimulation could be used as a non-invasive and efficacious approach to increase brain functions such as those related to cognitive and emotional dimensions. This innovative approach could lead to the development of non-invasive, performance-enhancing interventions in healthy humans and in those in need of neuropsychological rehabilitation.

1:54 **Reduced sociability is exhibited by alterations in scent marking and ultrasonic vocalizations after traumatic brain injury (TBI) in the developing mouse**. Bridgette D. Semple1, Zahra Adahman2, Christopher Hollingsworth2, Kayleen Gimlin1, Linda Noble-Haeusslein1,3 and A. Katrin Schenk2. 1, Departments of Neurological Surgery, 3Physical Therapy and Rehabilitation, University of California San Francisco, CA. 2, Department of Physics, Randolph College, Lynchburg, VA. As development of social behavior extends through adolescence, TBI at a young age may adversely affect the establishment of social skills. However, most preclinical studies fail to address social outcomes in experimental models. We previously evaluated social behaviors after TBI produced by a controlled cortical impactor

in mice at postnatal day (p)21, an age approximating the toddler-aged child. Of note, male brain-injured mice showed reduced social investigation in response to naïve age-matched males compared to sham controls, when tested at adulthood but not at adolescence. This parallels the emergence of cognitive deficits seen in this model and in brain-injured children. Recently, we have evaluated socio-sexual behaviors of male mice in response to female stimuli, again tested as adults after TBI at p21 (n=10/group). Brain-injured mice show a striking reduction in scent-marking to a novel female, despite normal baseline levels of urination and defecation. This behavior is unlikely due to physical or fear-related inhibition, as brain-injured mice show normal locomotion and anxiety in the open field arena. Preliminary results also reveal an abnormal profile of ultrasonic vocalizations produced by brain-injured mice in the presence of a female or female-scented bedding. Together, we propose that mice exhibit a social communication deficit when subjected to TBI in early life. Future studies will determine whether such changes are dependent on injury severity or age, as well as identification of underlying mechanisms, which may be targeted to improve psychosocial outcomes.

2:06 **Sodium selenate treatment reduces hyperphosphorylated tau and improves behavioral outcome in an animal model of repeated brain concussion**. Sandy Shultz, Xin Lin Tan, David Wright, Terence O'Brien, Department of Medicine (Royal Melbourne Hospital), Melbourne Brain Centre, University of Melbourne, Australia. Concussions account for the majority of traumatic brain injuries (TBI), and repetitive concussions can result in cumulative damage, neurodegeneration, and chronic neurological abnormalities. Hyperphosphorylated tau has been implicated in the pathogenesis of repeated concussion. Here we investigated whether treatment with sodium selenate, a drug that reduces the pathological hyperphosphorylation of tau by increasing the activity of the major tau phosphatase (PP2A), would reduce neurodegeneration and functional impairments in a rat model of repeated concussion. After repeated mild fluid percussion injuries, or sham-injuries, young-adult male Long-Evans rats were given continuous sodium selenate treatment (1 mg/kg/day), administered via subcutaneous osmotic mini-pump, for a period of three months. Cognitive, motor, and emotional impairments were assessed at three months post-injury. Anatomical magnetic resonance imaging and diffusion weighted imaging were used to assess structural damage and axonal injury at three months post-injury. Immunohistochemical and western-blot analyses were used to assess levels of hyperphosphorylated tau and related pathologies. The results demonstrated that continuous sodium selenate treatment reduced neurodegeneration and behavioural impairments after repeated concussions in the rat. These data indicate that sodium selenate has neuroprotective effects in a rat model of repeated concussion, and may represent a novel approach to treat these injuries.

2:18 **Social cognition in a 'two hit' model of psychosis: Male-specific additive effects of methamphetamine treatment and genetic depletion of brain-derived neurotrophic factor**. Manning, Elizabeth E. The Florey Institute of Neuroscience and Mental Health. van den Buuse, Maarten. The Florey Institute of Neuroscience and Mental Health. Methamphetamine (METH) users have an increased prevalence of psychosis and schizophrenia, including deficits in a number of cognitive domains. Brain-derived neurotrophic factor (BDNF) is implicated in the pathophysiology of schizophrenia, and the neuronal response to stimulant drugs. However, the role of BDNF in METH-induced psychopathology remains unclear. To address this, BDNF heterozygous mice (HETs) and wild-type (WT) littermates were treated with METH during late adolescence and tested in early adulthood for social cognition in the Crawley 3-chamber social interaction task and short-term spatial memory in the Y maze. Using Cleversys TopScan software, social approach behaviour was assessed by measuring chamber time and sniffing of the cups holding stranger mice, while spatial memory was assessed by measuring arm time. METH treatment altered social novelty preference in males (sex x METH x cup sniffing $p<0.05$). Further analysis in males revealed additive effects of METH treatment and BDNF depletion (METH x cup sniffing, genotype x cup sniffing $p<0.05$), and that METH-treated BDNF HETs did not show a preference to interact with a novel stranger over a familiar stranger. In contrast, all groups showed a significant preference to interact with a stranger mouse over an empty cup during the sociability phase. Short-term spatial memory in the Y maze was also unaffected by METH treatment and BDNF depletion in both sexes. These findings show that METH treatment during late adolescence and BDNF depletion have additive effects to disrupt social cognition in the 3-chamber task. This effect was male-specific, and short-term spatial memory was unaffected by these interventions. This 'two hit' model may add to our understanding of the neurobiology of social cognitive deficits in schizophrenia and METH-induced psychosis.

2:30 **Neuropeptide Mechanisms and Treatment Targets in Stress-Induced Psychiatric Disorders**. Patrick J. Ronan / Avera Research Institute / USD School of Medicine / VA Research Service. Sioux Falls, SD, USA. Stress plays a major role in the etiology and pathophysiology of a host of psychiatric disorders ranging from depression and addiction to anxiety disorders such as post traumatic stress disorder (PTSD). Corticotropin releasing factor (CRF) is a neuropeptide that is a key coordinator of an organism's multiple responses to stress: endocrine, autonomic and behavioral. Dysregulation of CRF signaling has been clearly implicated in a number of these stress-induced disorders. Orexin (ORX), also known as hypocretin, is more recently discovered neuropeptide that, like CRF, also appears to play a key role in arousal and stress responses. Early evidence from our lab and others suggests that aberrant signaling of the ORX system also plays a role in stress-induced disorders. In our lab we are seeking to better understand the molecular mechanisms underlying both normal signaling of these systems and dysregulation of these systems related to psychiatric disorders. We utilize a host of animal models and lab techniques to accomplish these goals. Highlights of recent work to be discussed include extensive characterization of the microanatomy of the CRF and ORX systems detailing their interaction both with each other as well as with other signaling systems in brain such as dopamine. We will present our

findings implicating ORX in an animal model of depression. We are now using genetic tools to further decipher its role in a wider range of models and will present these results. Also, we will discuss the development of a robust model of PTSD-like cue-induced binge ethanol drinking and the important role for CRF signaling in this behavior. We will also briefly discuss optogenetic strategies currently being used to better understand signaling of the CRF and ORX systems.

2:42 **Tail suspension test: Study of behavioral structure in male and female swiss mice**. Ana Paula Ramos Costa1, Evelyn Cristina da Silva Santos1, Cilene Lino-de-Oliveira2, Thereza Christina Monteiro De Lima1 1- Departament of Pharmacology, CCB, UFSC, Florianópolis, SC, 88049-900, Brazil. 2- Departament of Physiological Sciences, CCB, UFSC, Florianópolis, SC, 88049-900, Brazil. Depression is currently considered a life-threatening disease with a suicide rate of 15% among patients. Antidepressant drugs provide complete remission to about 50% of patients and cause several side effects. Therefore, animal models of antidepressant activity are valuable tools to better understanding the neurobiology of this disorder and to evaluate new antidepressant drugs. The tail suspension test (TST) has been one of the most used tests for this kind of evaluation mainly because of its ease of use. However, this test still lacks sensitivity and specificity, often leading to false positive or negative results. We here studied if the evaluation of a wider catalog of behaviors could overcome these limitations. Thus, the aim of the present study was to evaluate the structure of the behavior of male and female Swiss mice submitted to TST (n=50) applying a catalog comprising active and passive behaviors over the 6 min of the duration of the test. Animals were divided into 5 groups of 10 mice and were treated with NaCl 0.9% (control group), antidepressant drugs (imipramine, desipramine and fluoxetine, 30mg/kg, IP) or with a motor stimulant (caffeine, 30mg/kg, IP) 30 min prior TST. The behaviors assessed in the TST were immobility (total absence of movement), flexed immobility (the animal remains motionless holding his paws or his tail), diffuse movement (non-repetitive movements in all possible directions) and rhythmic movement (repetitive pendular movements). A complete sampling was performed over the period of either test, generating frequencies and durations of the behaviors. For the data of male mice, the temporal analysis of behaviors in the TST showed that active behaviors were more prevalent in the first 2 min of the test when the passive postures started to increase. The profile presented by females subjected to this test has some special features, such as the frequency of flexed immobility is larger than in males, regardless the phase of the estrous cycle. Antidepressants and caffeine showed the expected effects on mice in TST, i.e., a reduced immobility time. However, caffeine and antidepressants affected different pools of active behaviors in male mice (desipramine was the only treatment capable of increasing the time and frequency of rhythmic movement in TST; and caffeine was the only treatment which was able to increase the time of diffuse movement in TST) which allowed the discrimination between the two classes of drugs in TST. Moreover, the methodological changes in the data acquisition and data analysis allowed to distinguish antidepressant for stimulants drugs and open an opportunity to understand the difference in response to certain treatments that exists when the gender is compared. Acknowledgements: FAPESC, CAPES and CNPq.

2:54 **microRNAs as Novel Antidepressant Targets in Refractory Depression: Converging Effects of Ketamine and Electroconvulsive Shock Therapy**. Richard M. O' Connor1, Timothy G. Dinan2, 3 and John F. Cryan 1, 2 1Dept Anatomy and Neuroscience, 2Alimentary Pharmabiotic Centre, and 3Dept Psychiatry, University College Cork, Ireland. Despite being of benefit in a large number of patients current antidepressant drugs are hampered by a slow onset of action and a significant percentage of non-responders. Hindering the development of novel therapeutics is the fact that large gaps remain in our knowledge of the molecular pathophysiology underlying depression and in the molecular mechanisms of antidepressants. Acute administration of the NMDA receptor antagonist ketamine induces a rapid and persistent antidepressant effect with increased efficacy in treatment-resistant depression. Electroconvulsive shock therapy (ECT) is also employed in treatment-resistant depression. The molecular mechanisms underlying these therapies are not fully understood. MicroRNAs(miRNAs) are small regulatory RNAs increasingly seen as attractive drug targets given their ability to affect the expression of multiple genes. We hypothesised that miRNAs would be involved in early-life stress-induced pathology as well as in the action of antidepressant therapeutics. To this end early-life stress was induced in male Sprague Dawley rats by separating pups from their dams from postnatal days 2-12. This paradigm consistently produces depression-like behaviour. When rats reached maturity repeated ECS (85 mA/day /10 days), acute ketamine (10 mg/kg) and for comparison, chronic treatment with the selective serotonin reuptake inhibitor fluoxetine (10 mg/kg/day/21 days) were administered. 24hours following final treatment rats were sacrificed and the hippocampus removed microarray based miRNA profiling was conducted. Microarray analysis revealed early-life stress affected the expression of multiple hippocampal miRNAs. Antidepressant treatments reversed some of these effects including a stress-induced change to miR-451. Interestingly all three antidepressant treatments possessed more targets in stressed than in non-stressed animals. Ketamine and ECT possessed the highest number of common targets (43) suggesting convergence on common pathways. All three treatments possessed miR-598-5p as a common target. This demonstrates changes to hippocampal miRNA expression may represent an important component of stress-induced pathology and antidepressant action may reverse these.

3:06 **Investigating neuroendocrine changes and the impact of pre-treatment of Antalarmin on depressive-like behaviour in a rat model of global cerebral ischemia**. Patricia B. de la Tremblaye [1], Julie Raymond [1], and Hélène Plamondon [1], [1]Behavioral Neuroscience group, School of psychology, University of Ottawa, Canada. Considering the link between stress and the regulation of emotional behavior, and the occurrence of depression in an important subset of individuals following cardiac arrest and stroke, the current study aimed to characterize whether alterations of

glucocorticoid receptors, corticotropin releasing hormone (CRH) and CRH type 1 receptor (CRH-R1) expression are persistent 30 days post ischemia (Experiment 1). A second goal of this study was to assess the impact of pre-ischemic blockade of CRH-R1 receptors on emotionality and depressive-like behaviour occurring post-ischemia (Experiment 2). For both experiments, the four vessel occlusion model was used to induce a 10 minute global cerebral ischemia in male Wistar rats. Sham rats acted as controls. In Experiment 2, rats received an intracerebroventricular injection of the CRHR1 antagonist Antalarmin (2μg/2μl) or saline 30 minutes before ischemia or sham occlusion (N= 40, n = 10/group). Emotional and depressive-like behaviours were assessed using the social interaction, social preference, sucrose preference, and forced swim tests. Our findings revealed a persistent increase in GR, CRH and CRHR1immunoreactivity (ir) in the hypothalamic paraventricular nucleus 30 days following global ischemia while reduced expression of the same markers was present in the hippocampus. Reduced CRH-ir was also observed in the central nucleus of the amygdala in ischemic as compared to sham-operated rats. These alterations indicate persistent HPA axis dysfunctions following cerebral ischemia. These results complement recent observations from our lab showing elevated post testing CORT secretion associated with spatial memory impairments in the Barnes maze in ischemic animals and not present in sham rats or metyrapone-treated ischemic rats. Behavioural testing in Experiment 2 for the four animals groups treated with Antalarmin or saline is at the final stage. Together, these findings will shed light on the contribution of CRH and HPA axis hyperactivity to hippocampal neuronal injury, as well as cognitive and emotional impairments observed following brain ischemia.

3:18 **Trehalose induced antidepressant-like effects and autophagy enhancement in mice.** Einat H, Tel Aviv-Yaffo Academic College. The disaccharide trehalose was demonstrated to protect cells from hypoxic and anoxic injury and suppress protein aggregation. In-vivo studies with trehalose show cellular and behavioral beneficial effects in animal models of neurodegenerative diseases. Moreover, trehalose was shown to enhance autophagy, a process that had been recently suggested to be involved in the therapeutic action of antidepressant and mood stabilizing drugs. The present study was therefore designed to explore antidepressant and mood stabilizing activity of trehalose in animal models for depression and mania. Trehalose was chronically administered as a drinking solution to Black Swiss mice (a model of manic-like behaviors) or to ICR mice and their behavior evaluated in a number of tests related to depression or mania. The effects of trehalose were compared with chronic administration of the disaccharide maltose as well as with a vehicle (water) control. Chronic administration of trehalose resulted in a reduction of frontal cortex p62/beclin-1 ratio suggesting enhancement of autophagy. Trehalose had no mood stabilizing effects on manic-like behavior in Black Swiss mice but instead augmented amphetamine-induced hyperactivity, an effect similar to antidepressant drugs. In ICR mice, trehalose did not alter spontaneous activity or amphetamine-induced hyperactivity but in two separate experiments had a significant effect to reduce immobility in the forced swim test, a standard screening test for antidepressant-like effects. The results suggest that trehalose may have antidepressant-like properties. It is hypothesized that these behavioral changes could be related to trehalose effects to enhance autophagy.

1:30-3:30 **Oral Session 2: HIV and addiction. Chair: Mikhail Pletnikov**. *Guttenberg Suite*

1:30 **The role of αCaMKII autophosphorylation in the establishment of alcohol drinking behaviour in mice**. Christian P. Müller, Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University of Erlangen-Nuremberg, Schwabachanlage 6, 91054 Erlangen, Germany. The establishment of alcohol-addiction related behaviors requires a variety of learning-related molecular pathways. Alpha Ca2+/calmodulin dependent protein kinase II (αCaMKII) is a crucial enzyme controlling plasticity in the brain and learning and memory at behavioral level. The autophosphorylation of αCaMKII works as a 'molecular memory' for a transient calcium activation, thereby accelerating learning. We tested 23 single nucleotide polymorphisms (SNPs) in the CAMK2A gene for their association with alcohol dependence in a population of 1333 male patients with severe alcohol dependence and 939 controls. We found seven significant associations between CAMK2A SNPs and alcohol dependence, one of which in an autophosphorylation-related area of the gene. In parallel we found that alcohol drinking was initially diminished in αCaMKII autophosphorylation deficient αCaMKII T286A mice, but could be established at wild-type level after two withdrawal periods. The locomotor activating effects of a low dose alcohol (2 g/kg) were absent in αCaMKIIT286A mice, while the sedating effects of high dose (3.5 g/kg) were preserved. In-vivo microdialysis revealed that αCaMKII T286A mice showed no dopamine (DA) response in the nucleus accumbens to acute alcohol administration, but enhanced serotonin (5-HT) responses in the prefrontal cortex. The attenuated DA response in αCaMKII T286A mice was accompanied by altered c-Fos activation in a part of the ventral tegmental area. Together, our data suggest αCaMKII autophosphorylation as a facilitating mechanism in the establishment of alcohol drinking behavior by modulating the DA–5-HT balance in the response to alcohol.

1:42 **Environmental perturbation, inflammation and behavioral fatigue in healthy and virus-infected mice**. Linda A. Toth and Rita A. Trammell, Departments of Pharmacology (Toth) and Internal medicine (Trammell), Southern Illinois University School of Medicine, Springfield IL 62794. Infectious and inflammatory conditions are often associated with fatigue, exemplified in people by infection with or reactivation of Epstein-Barr virus (EBV). Murine gammaherpesvirus (MuGHV) is a natural pathogen of wild rodents that provides an experimental model for studying the pathophysiology of an EBV-like gamma-herpesvirus in mice. To evaluate this model with regard to fatigue and assessment of potential mechanisms that underlie exacerbation of fatigue during a chronic viral disease, we exposed

healthy and MuGHV-infected C57BL/6J and BALB/cByJ mice to novel environmental perturbations and measured the impact of these challenges on indices of behavioral fatigue and markers of inflammation. The data indicate that exposure of latently-infected mice to these situations during the normal somnolent phase is associated with behavioral signs consistent with fatigue during the subsequent active phase, despite an intervening rest period. Although basal cytokine and chemokine concentrations in serum showed relatively few infection-related differences, basal concentrations of some analytes differed significantly in lung of infected and uninfected mice. Furthermore, exposure to a social stress for 6 h was associated with inflammatory responses in both serum and lung regardless of infection status. Taken together, the data show that exposure of mice to mild environmental stress is associated with signs of systemic inflammation in a manner that is largely independent of genetic background or latent MuGHV infection, yet latently-infected mice also develop significant behavioral fatigue.

1:54 **Temporal processing demands implicate perceptual and gating deficits in the HIV-1 transgenic rat**. Rosemarie M. Booze, Landhing M. Moran, Charles F. Mactutus. University of South Carolina, Columbia, SC, USA. Impaired sensory gating, as measured by brainstem auditory evoked potentials (BAEP), is one of the earliest neurological abnormalities detectable in HIV-1-positive individuals. We utilized HIV-1 transgenic (Tg) rats, which express 7 of the 9 HIV-1 genes, to study prepulse inhibition (PPI) of the auditory startle response (ASR), a measure of sensorimotor gating. Ovariectomized female Fischer HIV-1 Tg and control rats (ns=41-43) were tested for PPI at three different ages (2, 4-6, and 6-8 months), using auditory and visual prepulses, an auditory startle stimulus, and interstimulus intervals (ISI) ranging from 0-4000 msec. Auditory and visual prepulse trial blocks were presented in counterbalanced order. For both auditory and visual prepulses, HIV-1 Tg animals exhibited a flatter ISI function, which did not sharpen with age, as it did in controls. At each age tested, auditory prepulses precipitated a temporal shift in peak inhibition in HIV-1 Tg animals relative to controls, whereas with visual prepulses, both groups displayed peak inhibition at the 40 msec ISI. A lack of perceptual sharpening with age and a relative insensitivity to the temporal dimension of sensorimotor gating are evident in the HIV-1 Tg rat prior to clinical signs of wasting. Deficits in sensorimotor gating may not only provide an early subtle diagnostic marker of HAND, but may also afford a great opportunity for development of potential therapeutics. Funded by NIH grants DA013137 and HD043680.

2:06 **Characterization of core components of executive function in HIV-1 Transgenic Rats**. Charles F. Mactutus, Landhing M. Moran, Rosemarie M. Booze. University of South Carolina, Columbia, SC, USA. Impairments of executive function are a prominent feature of HIV-1-associated neurocognitive disorders (HAND), despite the effectiveness of combination antiretroviral therapy (CART) in reducing viral load. We characterized the cognitive performance of 2-8 month-old female ovariectomized Fisher-344 HIV-1 transgenic (HIV-1 Tg) rats and non-transgenic controls (ns=41-43) using visual signal detection, visual discrimination/reversal, and extradimensional shift tasks to assess attention, behavioral flexibility, and set shifting, core components of executive function. All rats achieved 70% detection accuracy by 2 months, but 2x as many controls, relative to HIV-1 Tg animals, were able to meet this criteria after only 1 month. Shorter stimulus durations (1000, 500, 100 msec) increased task difficulty for both groups, however, the HIV-1 Tg group, relative to controls, failed to reliably detect the signal at the 500 and 100 msec durations. Visual discrimination learning and reversal learning were also impaired in HIV-1 Tg rats, albeit not differentially. The EDS shift to L-R position learning was readily mastered and well performed by the HIV-1 Tg rats. Chronic low level exposure to HIV-1 proteins in the HIV-1 transgenic rat, which resembles the suppression of infection in HIV-1 positive individuals under CART, primarily impairs the core executive function of attention, and thus supports the use of the HIV-1 transgenic rat to model HAND. Funded by NIH grants DA013137 and HD043680.

2:18 **The gut metabolite, S-equol, as a therapeutic for attentional deficits in HIV-1 transgenic rats**. Landhing M. Moran, Rosemarie M. Booze, Charles F. Mactutus. University of South Carolina, Columbia, SC, USA. HIV-1-associated neurocognitive disorders (HAND) afflict up to 50% of HIV-1-positive individuals despite the effectiveness of combination antiretroviral therapy (CART) in reducing the prevalence of more severe neurocognitive impairment (i.e., dementia). Deficits in executive function are a distinguishing feature of HAND in the CART era, decaying more rapidly during HIV disease progression than other cognitive domains. In the present study, ovariectomized female Fischer HIV-1 Tg (n=41) and control rats (n=43) were tested with a sustained attention task, a component of executive function. Rats were trained to discriminate signals (illumination for 100, 500, or 1000 msec duration) from non-signals (no illumination) and were reinforced with sucrose pellets for pressing the lever corresponding to each event (hits and correct rejections vs. misses and false alarms). A daily oral dose of S-equol (0.05, 0.1, or 0.2 mg, or vehicle), a metabolite produced via the gut microbiome following ingestion of soy isoflavone daidzein, was administered to determine its potential therapeutic effects. After 45 days of treatment, the HIV-1 Tg animals that received the 0.2 mg dose of S-equol missed significantly fewer signals across all stimulus durations compared to their pre-dosing performance. Their improvement was twofold that of the control group. The microbiota-gut-brain axis may be an important mechanism for potential therapeutics for HAND. Funded by NIH grants DA013137 and HD043680.

2:30 **ApoE genotype affects brain activity during nicotine use and withdrawal**. Rose, G.M., Coppens, R., Diggs, H., Kanneganti, R. and Gilbert, D.G. Southern Illinois University, USA. The ApoE4 allele is a risk factor for Alzheimer's disease. Recent studies have shown alterations in brain function even in young carriers of this allele. We evaluated whether ApoE genotype affected EEG and event-related potential (ERP) activity in young (mean age: 27 years

old) female smokers who were abruptly withdrawn from nicotine. EEG (19 channel; 10-20 system) was recorded, referenced to linked earlobe electrodes. Resting state EEG was sampled (eyes open and closed, 3 min each), then ERPs evoked using an auditory oddball task (80% 1 kHz, 20% 2 kHz tones; intertone interval 2000ms). Electrophysiological measures were taken one day prior to quitting and after 14 hours of nicotine abstinence. Genotyping was done from saliva samples. Data were collected from 44 ApoE3/E3 carriers and 13 ApoE3/E4 carriers. Subjects from the two genotypes did not differ in terms of their habitual nicotine intake (determined by pre-quit blood cotinine concentrations). Resting state EEG measures also did not differ between groups prior to nicotine abstinence. During withdrawal, all subjects showed more delta spectrum (2-4 Hz) power at Cz ($p = 0.01$); however greater EEG slowing occurred in the ApoE4 carriers ($p = 0.01$). ERPs to the oddball auditory stimulus were generally larger in ApoE4 carriers at frontal and parietal recording sites. Nicotine withdrawal enhanced ERP amplitudes at frontal sites (F3, Fz, F4; $p < 0.05$), with no difference between groups. In contrast, the late ERP (P3b) recorded at parietal sites was reduced after nicotine withdrawal in both groups ($p < 0.05$); the decrement was larger at P4 (right parietal cortex) in the ApoE4 group ($p < 0.05$). Thus, ApoE4 carriers exhibit greater EEG slowing and a larger P3b decrement subsequent to smoking cessation.

2:42 **Nicotine enhances the sign-tracking but not the goal-tracking response to a food-associated cue.** Paul J. Meyer, Department of Psychology, University at Buffalo, USA. Natural rewards, drugs of abuse, and their associated cues can act as signals to engage individuals in reward-seeking behavior. Further, some individuals attribute motivational value (incentive salience) to these cues, such that they become attractive (thereby eliciting approach towards them), and/or "wanted" (thereby acting as conditioned reinforcers). In the current study, we determined whether nicotine would alter the attractive and conditioned reinforcing properties of a food associated cue during a Pavlovian conditioned approach (PCA) paradigm. Fifteen minutes before each of five daily training sessions, rats were given either an injection of nicotine (0.4 mg base/kg) or saline. Rats then learned that an eight-second presentation of an illuminated lever predicted the delivery of a food pellet (25 trials per day). The number of lever contacts ("sign-tracking") and food magazine entries ("goal-tracking") was measured throughout training. Two days following PCA training, rats were given either an injection of nicotine or saline before being allowed to nose-poke for the presentation of the lever under extinction conditions. During PCA training, nicotine enhanced the degree of sign-tracking, but not goal-tracking. However, during the conditioned reinforcement test, neither previous treatment with nicotine nor nicotine challenge altered the conditioned reinforcing properties of the cue. These results suggest that nicotine enhances the attractiveness of reward-associated cues, but this effect is dissociable from its effects on conditioned reinforcement.

2:54 **Gut peptide GLP-1 and its analogue, Exendin-4, decrease alcohol intake and reward**. Rozita H Shirazi, Suzanne L Dickson, Karolina P Skibicka Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Sweden. Glucagon-like-peptide-1 (GLP-1) is a gut- and neuro-peptide with an important role in the regulation of food intake and glucose metabolism. Interestingly, GLP-1 receptors (GLP-1R) are expressed in key mesolimbic reward areas (including the ventral tegmental area, VTA), innervated by hindbrain GLP-1 neurons. Recently GLP-1 has emerged as a potential regulator of food reward behavior, an effect driven by the mesolimbic GLP-1Rs. Its role in other reward behaviors remains largely unexplored. Since a considerable overlap has been suggested for circuitry controlling reward behavior derived from food and alcohol we hypothesized that GLP-1 and GLP-1Rs could regulate alcohol intake and alcohol reward. We sought to determine whether GLP-1 or its clinically safe stable analogue, Exendin-4, reduce alcohol intake and reward. To determine the potential role of the endogenous GLP-1 in alcohol intake we evaluated whether GLP-1R antagonist, Exendin 9-39, can increase alcohol intake. Furthermore, we set out to evaluate whether VTA GLP-1R activation is sufficient to reduce alcohol intake. Rats injected peripherally with GLP-1 or Exendin-4 reduced their alcohol intake. Blockade of GLP-1 receptors alone resulted in an increased alcohol intake suggesting a contribution of endogenously released GLP-1. Furthermore, GLP-1 injection reduced alcohol reward in a CPP test. To evaluate the neuroanatomical substrate linking GLP-1 with alcohol intake/reward, we selectively microinjected GLP-1 or Exendin 4 into the VTA. This direct stimulation of the VTA GLP-1Rs potently reduced alcohol intake. Our findings implicate GLP-1 as a novel modulator of alcohol intake and reward. Considering that GLP-1 analogues are already approved for clinical use, this places the GLP system as an exciting new potential therapeutic target for alcohol use disorders. Grant support: Swedish Research Council for Medicine (2011–3054) and European Council FP7-KBBE-2010-4-266408 (Full4Health)

3:06 **Heavy episodic beer drinking enhances glutamate uptake in the prefrontal cortex of adolescent relative to adult C57BL/6J mice**. Karla Morales, Nicole Lugo, and Roberto I. Melendez University of Puerto Rico, School of Medicine, Dept. of Anatomy and Neurobiology, San Juan, Puerto Rico, 00936. Beer is one of the most widely abused alcoholic beverages worldwide, especially among human adolescents. Glutamatergic transmission in the prefrontal cortex (PFC) is essential for synaptic plasticity during adolescent brain development. Previous work has shown that intermittent every-other-day (EOD) access to ethanol (EtOH) solution appears suitable to study excessive (episodic) drinking in adolescent and adult C57BL/6J (B6) mice (Melendez 2011). We hypothesized that EOD access to 5% (v/v) beer and water for 2 weeks will promote greater beer drinking and preference in adolescent compared to adult male B6 mice (n=8/age). On the final test day, mice were given limited 3-hr access to beer, and trunk blood ethanol concentrations (BAC) were assessed. The kinetic constants Vmax (capacity) and Km (affinity) of [3H]-glutamate uptake were examined in PFC mixed synaptosomes; beer-naïve mice served as positive controls (n=4/age/treatment). EOD access to beer resulted in significant escalation of beer drinking and preference, in both age groups. The average escalated levels of beer

drinking and preference were significantly greater in adolescents (12.6 +/- 0.5 and 0.97 +/- .01) relative to adults (9.3 +/- 0.6 g/kg and 0.91 +/- .02, respectively). Limited access resulted in both greater beer intake and BAC in adolescent (5.4 +/- 0.4 and 24.8 +/- 4.1) than adults (3.4 +/- 0.2 g/kg and 8.9 +/- 2.6 mg/dl, respectively). There were no age differences in the Vmax and Km in naïve mice (13.0 +/- 0.8 pmol/mg protein and 5.6 +/- 0.6 μM, respectively). Interestingly, EOD beer drinking significantly elevated the Vmax in adolescent mice (24.9 +/- 1.7) compared to adults (15.8 +/- 1.4 pmol/mg protein) and beer-naïve mice; there were no differences in the Km for glutamate (5.5 +/- 0.3 μM). Elevated prefrontal glutamate uptake is likely the result of excessive synaptic glutamate transmission, which may further promote excessive drinking.

3:30-4:00 **Coffee/Tea Break.** *Tara Suite*

4:00-6:00 **Symposium: New horizons in nutrition, brain function and behavior. Chair: Robin B. Kanarek**. *Guttenberg Suite*

4:00 **Modeling the metabolic modulation of behavior – the case of b-vitamins and dementia.** Aron M. Troen, Hebrew University of Jerusalem, Israel. Animal models have been crucial for understanding the basis for the association between peripheral biomarkers of poor B-vitamin status and increased risk of dementia. However, while the immediate biochemical consequences of B-vitamin deficiencies are relatively well defined, downstream effects on brain and behavior may depend on metabolic integration and cross-talk between liver, brain and other organs. The extent to which peripheral metabolism is perturbed both quantitatively and qualitatively, may go a long way towards explaining the inconsistent behavioral results of nutritional interventions in both animal and human studies by our and other research groups. Greater consideration of the role of peripheral metabolism in determining brain and behavioral outcomes will help to improve the validity of animal models in the field of nutritional neuroscience, and may ultimately offer new targets for the prevention and treatment of age-associated cognitive decline.

4:30 **Omega-3 polyunsaturated fatty acids and depression.** Grace Giles, Tufts University, Medford, MA, USA. Depression is one of the most prevalent disorders worldwide. However, current pharmacological treatment options are only moderately more effective than placebo in treating the disorder. Omega-3 polyunsaturated fatty acid supplementation may reduce symptoms of major depressive disorder and perinatal depression. Although the results are often inconsistent, the majority of clinical trials and epidemiological studies suggest that intakes of polyunsaturated fatty acids are associated with depressive symptoms, such that omega-3 polyunsaturated fatty acid supplementation reduces depressive symptoms while a high ratio of omega-6-fatty acids to omega-3 fatty acids increases the risk of depression. It seems that omega-3fatty acid intake is more strongly associated with reduced depressive symptoms in women than men. Moreover, intake of the omega 3-fatty acid eicosapentaenoic acid has greater antidepressant effects than omega-3fatty acid docohexaenoic acid. This presentation will assess methodological considerations in exploring the relationship between omega-3fatty acids and behavior in depressed and healthy individuals, as well as the empirical evidence for this relationship.

5:00 **Creatine's role in brain function and affective behavior.** Kristen E. D'Anci, Department of Psychology, Salem State University, Salem, MA. U.S.A. Creatine has become one of the most widely used dietary supplements. Athletes use creatine to enhance muscle mass and increase strength and as an ergogenic aid to improve performance in sports involving high-intensity physical activity such as cycling, jogging, or rowing. In addition to its role in physical performance, creatine is important for the maintenance of cellular energy, and is critical for neural function. Changes in brain creatine levels, as measured using magnetic resonance spectroscope, are seen in depressed individuals and those exposed to drugs of abuse. These changes in brain creatine suggest that energy metabolism differs in these populations relative to healthy individuals. In this presentation, research demonstrating that creatine supplementation has protective effects on the brain functioning in animal models of neural damage, and in rats has the ability to function in a manner similar to antidepressant drugs will be reviewed. Moreover, recent studies indicating that creatine supplementation in humans can alter mood state and cognitive performance on stressful tasks that challenge the prefrontal cortex and can moderate responses to drugs of abuse such as amphetamine will be presented.

5:30 **Acute and longer term effects of breakfast consumption on behavior.** Andrew P Smith, Cardiff University. Conventional wisdom and growing experimental evidence indicated that breakfast may be the "most important meal of the day". This presentation will review research on the acute effects of consumption of breakfast on behavior and the longer term effects of habitual breakfast consumption. The presentation will cover methodological issues, underlying mechanisms and the practical implications of the results.

4:00-6:00 **Symposium: Broken clocks, inflammatory overload, and social pressures: Modeling stressors of the modern world and their effects on brain and behavior. Chair: Ilia Karatsoreos**. *Tara Suite*

4:00 **Good stress, bad stress, and the effects on neural and behavioral function.** McEwen, Bruce. The Rockefeller University, New York, NY. The brain is the central organ of stress and adaptation to stress because it determines what is threatening and initiates behavioral and physiological responses to the threat. In response to stressful

and other experiences, both the adult and developing brain possess a remarkable ability to show structural and functional plasticity including neuronal replacement, dendritic remodeling, and synapse turnover. This is particularly evident in the hippocampus, where all three types of structural plasticity have been investigated using morphological, molecular, pharmacological, electrophysiological and behavioral approaches. The amygdala and the prefrontal cortex, brain regions involved in anxiety and fear, mood, cognition and behavioral control, also show structural plasticity. Acute and chronic stress can cause an imbalance in the neural circuitry subserving these processes, and result in increased or decreased expression of these behaviors. In the short term, such as increased fearful vigilance and anxiety in a threatening environment, these changes may be adaptive; but, if the danger passes and the behavioral state persists along with the changes in neural circuitry, it can become maladaptive, and may need intervention with a combination of pharmacological and behavioral therapies, as is the case for chronic or mood anxiety disorders. Sex differences in the way the brain responds to stressors, as well as the effects of adverse early life experience, and how these interact with alleles of certain genes to produce lasting effects on the brain and body require urgent further exploration. While prevention is most important, the plasticity of the brain gives hope for therapies that take into consideration brain-body interactions.

4:30 **Clocks interrupted: Effects of sleep and circadian disruption on neural plasticity and behavior.** Karatsoreos, Ilia. Washington State University, Pullman, WA, USA. Circadian (daily) rhythms in physiology and behavior are phylogenetically ancient and are present in almost all plants and animals. In mammals, these rhythms are generated by a master circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, which in turn synchronizes "peripheral oscillators" throughout the brain and body in almost all cell types and organ systems. While circadian rhythms are phylogenetically ancient, modern industrialized society and the ubiquity of electric lighting has resulted in a fundamental alteration in the relationship between an individual's endogenous circadian rhythmicity and the external environment. The ramifications of this desynchronization for mental and physical health are not fully understood, though numerous lines of evidence are emerging that link defects in circadian timing with negative health outcomes. Our group has begun to explore animal models of circadian disruption to understand how disrupted brain and body clocks contribute to physiological and neurobehavioral changes that bear similarity to chronic stress, or how such states can alter the response to additional stressors. I will show that a mouse model of circadian disruption leads to loss of neural complexity in the prefrontal cortex, changes in prefrontal mediated behaviors, metabolic dysregulation, and altered immune responses. The role of circadian clocks in maintaining optimal behaivoral and physiologic function, and the consequences of circadian disruption for brain, behaviour and physiology will be discussed in the context of what we know about how stress can affect the brain and body.

5:00 **Chronic psychosocial stress effects on emotions, inflammatory state and adrenal functions: Reversal by oxytocin?** Inga D Neumann, Sebastian Peters, Stefan O Reber. Dept of Behavioural and Molecular Neurobiology, University of Regensburg, Germany. There is clinical evidence for a link between chronic psychosocial stress and the development of psychopathologies and inflammatory disorders. In our model of chronic psycho-social stress, i.e. exposure to chronic subordinate colony housing (CSC, 3 weeks), CSC mice show profound alterations in physiological, behavioural, neuroendocrine and immunological parameters (1). Accompanied by reduced body weight gain, thymus atrophy, and adrenal hypertrophy as established indicators of chronic stress, CSC mice show impaired glucocorticoid (GC) signalling and increased pro-inflammatory cytokine secretion from lymph node cells all contributing to the CSC-induced acute colitis. Further, CSC mice display a long-lasting increase in general anxiety, but no change in depression-related behaviours was found (2); a flattened circadian locomotor activity was also found after CSC exposure. Prior exposure to early life stress significantly amplifies the negative consequences of CSC on behavioural and physiological parameters (3). First pilot experiments indicate that chronic intracerebroventricular (icv) administration of oxytocin, a neuropeptide with anxiolytic and anti-stress effects (4), by osmotic minipumps during CSC exposure dose-dependently prevents some of the adverse effects of CSC. For example, icv oxytocin at low dose (1 ng/h) prevented CSC-induced thymus atrophy, adrenal hypertrophy and the hyper-secretion of interferon gamma. Thus, models of chronic psychosocial stress are particularly suitable to reveal complex behavioural and physiological consequences of chronic stress. [1] Reber S et al. Endocrinology 2007, 148:670-82. [2] Veenema AH. Endocrinology 2008, 149:2727-36. [3] Slattery DA et al. Psychoneuroendocrinology 2012, 37: 702-14 [4] Lukas M et al. Neuropsychopharmacology 2011, 36: 2159-68.

5:30 **Neuroimmune mechanisms underlying stress-induced immunosuppression.** Andrew Harkin, Niamh M. Curtin, Kingston H.G. Mills, Boyle NT, Thomas J. Connor. Neuroimmunology Research Group, Trinity College Institute of Neuroscience, Trinity College, Dublin 2, Ireland. Studies in humans and in animals indicate that psychological stress can modulate immune responses. Here we demonstrate that exposure to psychological stress (restraint stress) suppresses innate interferon (IFN)-γ production in mice following an in vivo lipopolysaccharide (LPS) challenge. IFN-γ signalling was also impaired by stress, as indicated by reduced STAT1 phosphorylation and reduced expression of the IFN-γ-inducible genes, inducible nitric oxide synthase (iNOS) and IFN-γ-inducible protein 10 (IP-10/CXCL10). Furthermore, restraint stress suppressed production of the IFN-γ inducing cytokine interleukin (IL)-12 and increased production of the anti-inflammatory cytokine IL-10, which can inhibit both IL-12 and IFN-γ production. However, using IL-10 knockout mice, we demonstrate that IL-10 does not mediate the suppressive effect of restraint stress on innate IFN-γ production. Restraint stress increased corticosterone concentrations in serum and spleen, and consistent with a role for glucocorticoids in the immunosuppressive actions of stress, pre-treatment with the glucocorticoid receptor antagonist

mifepristone completely blocked the stress-related suppression of IL-12 and IFN-γ production. In contrast, the stress-induced increase in IL-10 was blocked by pre-treatment with the β-adrenergic antagonist nadolol, demonstrating a key role for catecholamine-induced activation of β-adrenergic receptors in the ability of stress to enhance IL-10 production. Thus we demonstrate that stress suppresses production of the pro-inflammatory cytokines IL-12 and IFN-γ, and increases production of the anti-inflammatory cytokine IL-10 via parallel and independent neuroimmune pathways. Addition of exogenous IL-12 to LPS-stimulated spleen cells reversed the suppressive effect of both restraint stress and corticosterone on IFN-γ production, suggesting that reduced IL-12 production is a key event in stress-induced suppression of innate IFN-γ production. We also demonstrate that pre-treatment with the anxiolytic chlordiazepoxide attenuates the ability of stress to increase IL-10 and to suppress IL-12 and IFN-γ production. Repeated treatment with 2h restraint stress per day for 7 days also resulted in a suppression of IL-12 and IFN-γproduction and an increase in IL-10 when the animals were terminated at 1.5hpost stress (for IL-12 and IL-10) and at 8h post-stress (for IFN-γ). In contrast, exposure to repeated stress increased LPS-induced IL-12 and IFN-γproduction when assessed 24hr post termination of stress. In addition, repeated exposure to restraint stress inhibits the expression of the GR and theβ2-AR when assessed 24hr post stressor exposure and also suppresses LPS-induced IL-12 and IFN- production in response to the GR agonist cocticosterone and the β2-AR agonist salbutamol. Thus the immediate immunosuppressive actions of stress are followed by a pro-inflammatory state which is most likely a consequence of GR and β2-AR down-regulation. These pro-inflammatory actions may explain the ability of stress to exacerbate the clinical courses of certain autoimmune diseases.

6:00-8:00 **Break**

8:00-10:00 **Poster Session 2: Behavioral pharmacology and addiction models.** *Guttenberg Suite*

58. **Exposure to oxytocin during adolescence produces long-term impairments in sociosexual behaviors in male rats**. Harding, SM and Andreychik, MR. Fairfield University, CT, USA. Oxytocin (OT) is a neuropeptide that has been implicated in the development and regulation of healthy social interactions with sexual partners, offspring, and same-sex peers. Its potential use as a drug therapy for clinical conditions with social deficits, including autism and schizophrenia, has recently been a topic of discussion and intense research. However, the long-term effects of OT use, particularly during critical periods of brain development when the potential to modify behavior is high, have not yet been fully examined. The present study tested the effects of OT exposure in rats during adolescence on sexual performance and social components of reproduction (sociosexual behaviors) in adulthood. Twenty male Long Evans rats were pair-housed and assigned to OT (1 mg/kg, n=10) or Control (saline, 1 mg/kg, n=10) groups, receiving i.p. injections daily throughout adolescence (P34-P47). Behavior was assessed in adulthood using copulation tests to measure sexual performance, and partner preference tests and tests for 50kHz vocalizations and scent marking to measure sociosexual behaviors. Only minor differences between groups were observed in copulation tests, suggesting negligible effects of early OT exposure on sexual performance. However, rats receiving OT in adolescence showed significant impairments in partner preference, and emitted fewer 50kHz vocalizations and produced fewer scent marks compared to Controls. Taken together, these data suggest that exposure to OT during critical developmental periods can have long-term consequences on social aspects of reproduction. These findings are consistent with central and peripheral studies that have been done in other species, and should raise awareness and serious consideration about the long-term effects of OT therapy during adolescence.

59. **Decision making in methamphetamine-treated rat.** Hiroyuki Mizoguchi,[1] Kazuya Fukumoto,[1] Tian Wang,[2] Jun Sato1,[1] Kiyofumi Yamada[2] [1]Futuristic Environmental Simulation Center, Research Institute of Environmental Medicine, Nagoya University, Nagoya 464-8601, Japan. [2]Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan. Decision making in complex and uncertain situations is a fundamental adaptive process resulting from the integration of several executive functions. Impaired decision-making is a symptomatic feature of a number of psychiatric disorders such as addiction. In general, drug abusers show a propensity to prefer actions associated with large short-term gains but long-term losses preferentially to those associated with small but long-term gains. They are more likely to select risky options and show an altered temporal horizon of risks and benefits. However, it is unknown whether decision-making dysfunctions and their underlying neural substrates are preexisting condition and contribute to the initiation of drug use or are a consequence of the repeated use of these drugs. To clarify the underlying neurobiology of decision-making in neuropsychiatric disorders, we conducted a study in methamphetamine-treated rats by using a rodent gambling test based on uncertainty and conflicting choices. Control rats chose the small reward/low risk arms. Following chronic treatment, methamphetamine-treated rats chose large reward/high risk arms. These results suggest that methamphetamine affects the decision-making based on reward and risk in rats.

60. **Effects of maternal stress and perinatal fluoxetine exposure on behavioural outcomes of adult offspring**. Veronika Kiryanova[1], Sara Iablokova[1], & Richard H. Dyck[1,2,3] [1]Department of Psychology, and [2]Hotchkiss Brain Institute, and [3]Cell Biology and Anatomy; University of Calgary, Calgary, Alberta, Canada. Women of child-bearing age are the population group at highest risk for depression. Selective serotonin reuptake inhibitors (SSRIs) are the medication of choice for the treatment of depression and other psychiatric disorders, especially during

pregnancy. Fluoxetine (Flx) is the most widely prescribed SSRI, with 2.1% of all pregnant women using Flx throughout, or at some point during pregnancy. While maternal stress, depression, and Flx exposure have been shown to effect neurodevelopment of the offspring, separately, combined effects of maternal stress and Flx exposure have not been extensively examined. The present study investigated the effects of maternal stress and perinatal exposure to the SSRI Flx on the behaviour of male and female mice as adults. METHODS: C57BL/6 dams exposed to chronic unpredictable mild stress from embryonic (E) day 4 to E18 and non-stressed dams were administered Flx (25 mg/kg/d) in the drinking water from E15 to postnatal (P) day 12. A separate control group consisted of animals that were not exposed to stress or Flx. At two months of age, the male and female offspring of mothers exposed to prenatal stress, perinatal Flx, prenatal stress and Flx, or neither stress nor Flx, went through a comprehensive behavioral test battery. The behavioural battery included tests of cognitive abilities, memory, aggression, anxiety, sensorimotor information processing, and exploratory and risk assessment behaviours. RESULTS: Maternal Flx treatment led to detectible brain levels of Flx in the offspring and significantly altered pup brain levels of serotonin. While perinatal exposure to Flx increased aggressive behavior in the adult male offspring, prenatal maternal stress decreased aggressive behavior in the offspring. Interestingly, combination of stress and Flx normalized aggressive behavior in the male offspring. Furthermore, Flx treatment led to decrease in anxiety-like behavior in male offspring. Perinatal stress increased prepulse inhibition in the female offspring and led to hyperactivity of both male and female offspring of stressed mothers. The results of the current study were sex specific and may indicate differential actions of prenatal stress and fluoxetine on male and female mice. Support Contributed By: NSERC PGS-D, AIHS (VK), CIHR summer (SI) scholarships and NSERC Discovery and CIHR operating grants (RHD).

61. **Changes in endocannabinoid system may be involved with depressive-like behavior in streptozotocin-induced diabetic rats.** de Morais, H.; Pasquini, C.S; da Silva, L.M.; Maria-Ferreira, D.; Cunha, J.M.; Zanoveli, J.M. Department of Pharmacology, Division of Biological Sciences, Federal University of Paraná, Curitiba/PR. Previous studies have described that increase of endocannabinoid, such as anandamide (AEA), in brain areas demonstrated improvement in mood-related behaviors. Although the dysregulation in the endocannabinoid system can contribute to the development of diabetes and its complications, like depression, the mechanism involved in the association of diabetes and depression has not been elucidated yet. To investigate further this issue, rats were treated with citrate buffer (10 mM, pH 4.5; normoglycemic group-N) or streptozotocin (50 mg/kg, i.p.; diabetic group-DBT) and 4 weeks after, all animals were submitted to a treatment with AEA (0.001, 0.005, 0.01 mk/kg, ip) or vehicle (VEH) before the forced swimming test (FST). After the test, both N and DBT rats were euthanized and the hippocampus (HIP) and pre-frontal cortex (PFC) were dissected for further glutathione (GSH) levels quantification, an oxidative stress parameter. As a positive control to the antidepressant-like effect, both experimental groups were treated with imipramine (IMI; 15mg/kg, ip). When compared to N rats, DBT animals showed hyperglycemia, reduction in weight gain, depressive-like behavior, GSH levels decreased and no change in locomotor activity. Moreover, the treatment of DBT rats with AEA (0.005 mk/kg) induced a significant ameliorate in depressive-like behavior as well restored the GSH levels to normal levels. In contrast, AEA was not able to alter these behavioral and biochemical parameters in N rats. Differently, IMI treatment prevented the depressive-like effect in both N and DBT animals. Finally, IMI and AEA treatments were not able to alter the weight gain reduced as well the hyperglycemia observed in DBT animals. This study indicated that AEA treatment in DBT animals exerts antidepressant-like effect as well neuroprotector effect in the brain areas related to depression. The present data also suggest that a dysregulation in the endocannabinoid system can be involved in the mechanism linking the diabetes to depression. Financial Support: CAPES, CNPq, Brazil

62. **Developmental fluoxetine exposure affects hippocampal neurogenesis in adult rat offspring**. Ine Rayen1,3, Harry W.M. Steinbusch1,3, Jodi L. Pawluski1,2,3;1School for Mental Health and Neuroscience, Maastricht University, Universiteitssingel 50, 6229 ER Maastricht, The Netherlands; 2University of Liège, GIGA-Neurosciences, 1 avenue de l'Hôpital (Bat. B36), B-4000 Liège, Belgium; 3EURON, European Graduate School for Neuroscience. During pregnancy and postpartum, 20% of women are affected by depression and this is a growing health concern. Selective serotonin reuptake inhibitor (SSRIs) medications are popular treatments for maternal depression, however, the effect of maternal depression and perinatal SSRI exposure on offspring neural development needs further investigation. Recent work we have done has shown that developmental fluoxetine exposure reverses the effects of prenatal stress on hippocampal neurogenesis during adolescence. Therefore, the goal of this study was to determine the role of exposure to fluoxetine during development on plasticity in the adult hippocampus. To do this, prenatally stressed and non-stressed Sprague-Dawley rat offspring were exposed, via lactation, to either fluoxetine or vehicle beginning on postnatal day 1. Four groups of male and female offspring were used: 1) prenatal stress + fluoxetine, 2) prenatal stress + vehicle, 3) fluoxetine alone, and 4) vehicle alone. Brains of adult male and female offspring were analyzed for levels of cell proliferation (Ki67-ir) and new cell survival (3 weeks after BrdU injection) in the hippocampus. Preliminary data shows that developmental fluoxetine exposure significantly decreased the density of proliferating cells in the hippocampus of adult offspring exposed to prenatal stress. Interestingly, this effect was more pronounced in adult male offspring. These results provide important insights in the long-term developmental effects of maternal adversity and developmental fluoxetine exposure on neural plasticity in male and female offspring.

63. **Neurogenesis is not required for lithium's mood stabilizing-like effects**. Kara NZ, Agam G, Einat H. Dept. of Clinical Biochemistry and Pharmacology, Ben-Gurion University of the Negev and School of Behavioral Science, Tel Aviv-Yaffo Academic College. Cellular plasticity and resilience are now considered core research area in the field of affective disorders in general and bipolar disorder in particular. In this context, it has been suggested that deficiencies in hippocampal neurogenesis, may, at least in part, underlie the pathophysiology of bipolar disorder and that the therapeutic effects of mood stabilizers are related to their effects to enhance neurogenesis. In rodents, chronic treatment with the prototypic mood stabilizer lithium is known to increase dentate-gyrus neurogenesis and to induce mood stabilizing-like effects in behavioral tests. The present study was therefore designed to explore the role of neurogenesis in the therapeutic-like behavioral effects of chronic treatment with lithium in mice. To achieve this objective, the study tested the effects of inhibition of cellular proliferation (and therefore neurogenesis) on the behavioral effects of lithium in two animal models, the amphetamine-induced hyperactivity model of mania and the forced swim test model of depression. Our results demonstrate that arresting neurogenesis with the cytostatic agent MAM did not influence the behavioral effects of lithium in animal models related to the drug's mood stabilizing-like activity including the forced swim test and the amphetamine-induced hyperactivity test. These results suggest that the effects of lithium in these models are independent of its effect to induce neurogenesis. Namely, the results of the present study do not support the hypothesis that lithium-induced neurogenesis mediates the drug therapeutic effects.

64. **Effects of early life environmental enrichment on behavioural responses and BDNF levels of an animal model of schizophrenia – the SHR strain**. Santos, CM 1 3; Peres, FF 2 3; Gouvea, DG 2 3; Vendramini, AM 2 3; Levin R 2 3; Calzavara, MB 1 3; Abílio, VC 1 2 3 1: Departament of Psychiatry, Federal University of Sao Paulo - UNIFESP 2: Department of Pharmacology, Federal University of Sao Paulo – UNIFESP 3: Laboratório Interdisciplinar de Neurociências Clínicas - LiNC, Federal University of São Paulo - UNIFESP. Schizophrenia is a highly disabling mental disorder. Its pathophysiology is not completely elucidated, but changes in brain-derived neutrophic factor (BDNF) appear to be associated. Environmental enrichment has been suggested to increase BDNF levels and to improve some cognitive deficits. In this study, we aimed to evaluate a possible beneficial effect of early and long-term exposure to Enriched Environment (EE) on an animal model of schizophrenia recently characterized by our group - the SHR strain. Young male Wistar rats (WR) and SHR (26-29 PND) were housed for 6 weeks in two different conditions: in large cages (10 animals/cage) containing objects of different colors, forms and materials that was changed 3 times/week (EE condition) or in standard cages (5 animals per cage – Control condition). Behavioral evaluations were performed at 5 months of age: contextual fear conditioning (CFC), prepulse inhibition of startle (PPI) and spontaneous alternation (SA). Serum was collected to quantify BDNF. As previously shown, SHR present deficits in these behavioral tasks. EE was able to prevent the SA deficit in this strain. Additionally, EE impaired CFC. BDNF levels were increased in SHR and EE did not modify it in either strains. In conclusion, EE can be a potential strategy to prevent some behavioral deficits associated with schizophrenia. Considering the opposite effects of different BDNF isoforms (not evaluated in this study), further analyses are necessary to better understand their possible role in the beneficial effect of EE.

65. **Effects of cannabinoid drugs on prepulse inhibition of startle in an animal model of schizophrenia: The SHR (Spontaneously Hypertensive Rats) strain**. 1,2 Levin, R.; 1,2 Peres, F.F.; 1,2 Almeida, V.; 2 Calzavara, M.B.; 3 Zuardi, A.W.; 3 Hallak, J.E.; 3 Crippa, J.A.; 1,2 Abílio, V.C. 1 Department of Pharmacology, Federal University of São Paulo - UNIFESP, 2 Laboratório Interdisciplinar de Neurociências Clínicas, Federal University of São Paulo - UNIFESP, 3 Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo - USP. Clinical and neurobiological findings suggest that cannabinoids and the endocannabinoid system are implicated in schizophrenia. Recently, we found that the Spontaneously Hypertensive Rats (SHR) present many behavioral changes that are specifically reverted by antipsychotic drugs and potentiated by proschizophrenia manipulations. Based on these findings, we have suggested this strain as an animal model of schizophrenia. The aim of this study is to evaluate the effects of cannabinoid drugs on the deficit of prepulse inhibition of startle (PPI), the main paradigm used to study sensorimotor gating impairment related to schizophrenia, presented by the SHR strain. The following drugs were used: 1) WIN55212,2 (cannabinoid agonist), 2) rimonabant (cannabinoid antagonist), 3) AM404 (endocannabinoid uptake/metabolism inhibitor) and 4) cannabidiol (a non-psychotomimetic compound of Cannabis sativa). Male adult Wistar rats (WR) and SHR (8-12/strain/drug) were treated with vehicle or different doses of WIN55212 (0.3, 1 or 3 mg/kg – experiment 1), rimonabant (0.75, 1.5 or 3 mg/kg – experiment 2), AM404 (1, 5 or 10 mg/kg – experiment 3) or cannabidiol (15, 30 or 60 mg/kg – experiment 4). Thirty minutes later, the animals were submitted to the PPI test. In all experiments, vehicle-treated SHR showed a decreased PPI when compared to WR. This deficit was reversed by 1 mg/kg WIN and 30 and 60 mg/kg cannabidiol. Conversely, 0.75 mg/kg rimonabant tended to decrease PPI response in SHR strain whereas AM404 did not modify it. Our results reinforce the role of endocannabinoid system in the sensorimotor gating impairment related to schizophrenia and point to cannabinoid drugs as potential therapeutic strategies. Funding Acknowledgement: CNPq

66. **The 5-HT1A/1B receptor agonist eltoprazine has anti-impulsive properties and alters brain monoamine levels without enhancing brain stimulation reward**. J. Prins, F.S. Van den Bergh, R. Dupree, G.A.H. Korte-

Bouws, K.G.C. Westphal, R.S. Oosting, B. Olivier, S.M. Korte, Division of Pharmacology, Utrecht University, The Netherlands. High levels of impulsivity are associated with psychiatric disorders such as substance abuse disorders, aggression and attention-deficit hyperactivity-disorder (ADHD). Impulsivity can be broadly divided into two categories: i) response inhibition refers to the suppression of inappropriate actions, ii) impulsive choice refers to the ability to wait for a large reward (i.e. an immediate small reward is favored over a delayed and large reward). Alterations in monoaminergic neurotransmission is highly associated with these different types of impulsivity and pharmacological treatment of impulsivity (e.g. in ADHD) mainly targets monoamine systems. The 5-HT1A/1B receptor agonist, eltoprazine is known to inhibit impulsive aggression, and seems effective in treating symptoms of ADHD in a placebo-controlled phase II clinical trial. But its mechanism of action is not well understood. In the current study we investigated dose-related effects of eltoprazine on extracellular monoamine and metabolite concentrations in the medial prefrontal cortex (mPFC), lateral orbitofrontal cortex (lOFC) and nucleus accumbens (NAc), because these brain areas are involved in impulsivity and reward. Furthermore, we studied the effect of eltoprazine on response inhibition and impulsive choice with the stop-signal reaction time task and delayed reward task, respectively. Moreover, we also assessed the effects of eltoprazine on brain reward circuitry in an intracranial self-stimulation (ICSS) paradigm. Eltoprazine decreased response inhibition and increased the choice for large reward. Surprisingly, eltoprazine increased ICSS thresholds, suggesting a lowering of brain reward functioning. Microdialysis data showed a dose-dependent increase in extracellular levels of DOPAC and HVA and decreased 5-HT and 5-HIAA concentrations in the three brain areas. Furthermore, in the mPFC and lOFC, but not in the NAc, significant increases in NE and DA were found, demonstrating a clear 5-HT-DA and 5-HT-NE interaction. From these data we can conclude that the 5-HT1A/1B receptor agonist eltoprazine has anti-impulsive properties, and alters brain monoamine concentrations without enhancing brain stimulation reward.

67. **Acute prosocial effects of peripherally administered oxytocin, MDMA and their combination in rats: A possible common mechanism of action involving the V1A receptor**. Linnet Ramos, Callum Hicks, Richard Kevin, Alex Caminer, Iain S. McGregor, School of Psychology, Brennan MacCallum Building, University of Sydney, Sydney, NSW 2006, Australia. The role of the neuropeptide oxytocin (OT) in social behaviors continues to be of great interest. Surprisingly, little evidence exists for acute social effects of peripherally administered OT in animal models. However, the robust social effects of the party drug MDMA are well documented in rats and are thought to involve oxytocin. Here we directly compared the social effects of peripherally administered OT and MDMA, and examined the role of the vasopressin V1A receptor in these effects. Adult male Long Evans rats were tested in a social interaction paradigm after OT (0.1, 0.5, 1 mg/kg, IP), MDMA (5 mg/kg, IP), or a low dose combination of OT (0.25 mg/kg) and MDMA (2.5 mg/kg). Rats were paired with weight matched; unfamiliar, male conspecifics given the same drug treatment, and were tested for 30 min. Rats treated with OT (0.5mg/kg) and MDMA (5 mg/kg) or their combination showed an increase in adjacent lying and a reduction in anogenital sniffing. Interestingly, both OT and MDMA-induced adjacent lying were inhibited by the V1A receptor antagonist SR49059 (1 mg/kg). A second study used a social preference test, where male Long Evans rats were placed in a novel arena and presented with an object stimulus (empty wire cage) for 4 min followed by a social stimulus (cage containing unknown male conspecific) for 4 min. MDMA (5 mg/kg, IP) and OT (0.5 mg/kg, IP) treated rats showed a greater preference for the social stimulus than controls, further underlining the prosocial effects of both compounds. Experiments involving antagonism of OT and MDMA effects with SR49059 and the oxytocin antagonist Compound 25 are currently underway. Overall, our results to date suggest there may be a common mechanism between OT and MDMA in stimulating social behaviors that involves the vasopressin V1A receptor system.

68. **Cannabidiol effects in the prelimbic cortex depend on 5-HT1A receptors and previous stress experience**. Manoela V Fogaça1, Alline C Campos2, Fernando MCV Reis3, Francisco S Guimaraes1 1Dept. Pharmacology, FMRP, Center for Interdisciplinary Research on Applied Neurosciences, 3Lab. of Psychobiology, FFCLRP, USP, 2Clinical Medical Dept., School of Medicine, UFMG, Brazil. Cannabidiol (CBD) is a non-psychotomimetic phytocannabinoid with anxiolytic properties. Previously we showed that CBD administration into the prelimbic (PL) medial prefrontal cortex attenuates freezing in a contextual fear conditioning model. To further explore the neural basis of its action CBD was bilaterally injected into the PL of male Wistar rats submitted to the elevated plus maze (EPM) model of anxiety. CBD (30 nmol) induced an anxiogenic-like effect (represented by a decrease in open arm exploration). The dose response curve was U-shaped, with lower (15 nmol) and higher (60 nmol) doses being ineffective. CBD anxiogenic effect turned into an anxiolytic one when the animals were forced restraint for two h 24 h before the EPM test. Both the anxiolytic and anxiogenic effects of CBD were blocked by pretreatment with WAY100635 (0.37 nmol), a selective 5HT1A receptor antagonist. This drug also prevented the attenuation of contextual fear induced by intra-PL injection of CBD. Pre-restraint stress treatment with metyrapone (70mg/kg), a corticosterone synthesis inhibitor, prevented the anxiolytic effects of CBD in stressed rats. Our results indicate that CBD modulation of anxiety-like behavior in the PL depends on previous stress experience of the animals and is mediated by facilitation of local 5-HT1A-mediated neurotransmission. Financial support: Fapesp, CNPq.

69. **Knockdown of glutamate receptor interacting protein (GRIP) within the nucleus accumbens enhances reinstatement of cocaine seeking and alters synaptic plasticity.** Briand, L.A., Kimmey, B., Ortinski, P.I., Huganir, R.L. and Pierce, R.C., Departments of Psychiatry and Pharmacology, The University of Pennsylvania, Philadelphia, PA 19104. A growing body of evidence indicates that trafficking of AMPA glutamate receptors n the nucleus accumbens is critically involved in reinstatement of drug seeking, an animal model of relapse. Following cocaine self-administration, there is an increase in GluA2-lacking AMPA receptors at the synapse and disruption of GluA2 subunit-containing AMPA receptor internalization in the nucleus accumbens attenuates reinstatement behavior and measures of cocaine craving. However, the role of individual trafficking proteins in reinstatement is unclear. One such protein, glutamate receptor interacting protein (GRIP), is thought to stabilize GluA2 subunits at the synapse. Therefore, we examined the effect of a conditional deletion of GRIP within the nucleus accumbens on cue-induced reinstatement of cocaine seeking. GRIP was conditionally deleted by microinjecting a Cre recombinase-expressing virus into the nucleus accumbens of floxed-GRIP mice. GRIP deletion did not alter the ability of the mice to acquire the operant behavior, as evidenced by no change in acquisition of food self-administration. Additionally, no differences were seen between GRIP knockout and wildtype mice on cocaine self-administration behavior or extinction. However, we demonstrate a specific increase in cue-induced reinstatement of cocaine seeking following GRIP knockdown in the nucleus accumbens, which is not seen with food seeking. These changes in reinstatement occurred alongside changes in synaptic AMPA receptors. We also found that GRIP knockdown blocked LTD in the NAc, similar to what is seen in wildtype mice after cocaine self-administration and withdrawal. These results suggest that GRIP, by regulating plasticity in the nucleus accumbens, plays a critical role in the reinstatement of cocaine seeking.

70. **Inhibition of Ventral Pallidum Projection to VTA Blocks Cue-Triggered Cocaine Seeking**. Stephen V. Mahler (MUSC), Elena M. Vazey (MUSC), Jennifer Kaufling (MUSC), Bryan L. Roth (U North Carolina), Gary Aston-Jones (MUSC). Designer receptors exclusively activated by designer drugs (DREADDs) are synthetic G-protein coupled receptors that are inert, except in the presence of their agonist, CNO (which is inert in the absence of DREADDs). DREADD-expressing neurons can therefore be experimentally controlled in a highly selective, "lock-and-key" manner. Although light-activated opsins are preferable for experiments requiring precise temporal (milliseconds to seconds) control of neuronal activity, DREADDs can be preferable when extended periods of inactivation are desired (minutes to hours). In addition, DREADDs do not require tethering of animals to a light source, an advantage when animals perform complex behaviors. Here, we examined the role of ventral pallidum (VP) and its projection to ventral tegmental area (VTA) in reinstatement of cocaine seeking. We used an hM4D Gi-coupled DREADD construct, expressed under control of a synapsin promoter via lentiviral neurotransduction in vivo in rats. First, we examined the necessity of VP for reinstatement elicited by either cocaine-associated cues or a cocaine priming injection. We bilaterally transfected VP neurons with the DREADD viral vector, trained rats on cocaine self-administration and extinction, and then systemically administered several doses of the DREADD agonist CNO during cue-induced or cocaine primed reinstatement sessions. We found that CNO dose-dependently blocked cue-induced, but not cocaine-primed reinstatement of cocaine seeking, indicating that VP activity is required for cues to trigger cocaine seeking. We previously observed that VP projections to VTA are robustly Fos activated during cue-induced reinstatement behavior, so we next sought to examine whether this specific projection is necessary for cue-induced reinstatement of cocaine seeking. For this, we again bilaterally transfected VP neurons with the hM4D DREADD, allowed time for DREADD transport to axonal terminals in VTA (5-6 weeks), and implanted bilateral cannulae into VTA. Prior to cue-induced or cocaine-primed reinstatement sessions, we microinjected CNO into VTA to specifically inhibit DREADD-expressing VP terminals. Again, this attenuated cue-induced, but not cocaine-primed reinstatement. No similar effects were seen in animals after inhibition of the nearby VP-substantia nigra projection. These findings demonstrate that i) DREADDs are a useful means of modulating neuronal activity in behavioral experiments, ii) DREADDs can be used to locally inhibit terminals of projections from transduced neurons, and iii) ventral pallidum projections to VTA are crucial for cue-induced, but not cocaine-primed reinstatement. Supported by PHS grants R37 06214, F32 DA026692 and K99 DA035251.

71. **Effects of cannabinoid and vanilloid drugs on positive and negative-like symptoms in an animal model of schizophrenia – the SHR strain.** Almeida, Valéria 1,2; Peres, Fernanda Fiel 1,2; Levin, Raquel 1,2; Suiama, Mayra 1,2; Abílio, Vanessa Costhek 1,2. 1 - Department of Pharmacology, Federal University of São Paulo - UNIFESP, 2 - Laboratório Interdisciplinar de Neurociências Clínicas, Federal University of São Paulo - UNIFESP. The endocannabinoid and the vanilloid systems seem to be implicated in the pathophysiology of schizophrenia. Recently, we have suggested the SHR (Spontaneously Hypertensive Rats) strain as a new animal model to study schizophrenia: among other schizophrenia-like alterations, it presents a deficit in social interaction (SI) and hyperlocomotion (modelling negative and positive symptoms of the disease, respectively) that are ameliorated by antipsychotics. The aim of this study is to evaluate the effects of cannabinoid and vanilloid drugs on these behavioral alterations. Male adult Wistar rats (WR) and SHR (10-12/strain/drug) were treated with vehicle or 0.1, 0.3 or 1 mg/kg WIN55-212 (CB1 agonist – experiment 1), 1, 5 or 10 mg/kg AM404 (anandamide uptake/metabolism inhibitor – experiment 2), or 0.1, 0.5 or 2.5 mg/kg capsaicin (TRPV1 agonist – experiment 3). Thirty minutes later, pairs of unfamiliar rats of the same strain and treatment were placed in an open-field for 10

minutes and SI and locomotion were scored. SHR presented a decrease in SI time and an increase in locomotion when compared to WR. WIN55-212 induced a decrease in locomotion (1mg/kg) and in SI (0.1 and 0.3mg/kg) of WRs, while the dose of 1mg/kg increased the SI of SHR. AM404 increased SI and decreased locomotion of SHR (5mg/kg), and decreased SI and increased locomotion in WR (1mg/kg). Capsaicin decreased locomotion (0.1 and 0.5mg/kg) of WR, and increased the SI and decreased locomotion of SHRs(2.5mg/kg). In conclusion, cannabinoid and vanilloid drugs present different effects on positive- and negative-like behaviors depending on the strain and the dose. These results reinforce the important role of these systems in the pathophysiology of schizophrenia and as therapeutical targets for its treatment. Funding acknowledgement: Fapesp and CNPq.

72. **Overactivation of muscarinic cholinergic receptors leads to long-term anxiogenic responses associated with hippocampal theta rhythm activity and HPA axis alterations**. Hoeller AA[1], Spiga F[2], Lightman SL[2], Collingridge GL[3], Bortolotto ZA[3], De Lima TCM[1]. [1]Laboratory of Neuropharmacology, Department of Pharmacology, Federal University of Santa Catarina, Florianópolis, 88049-900, Brazil. [2]Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, School of Clinical Sciences, University of Bristol, Dorothy Hodgkin Building, Bristol BS1 3NY, UK. [3]MRC Centre for Synaptic Plasticity, School of Physiology and Pharmacology, University of Bristol, Dorothy Hodgkin Building, Bristol BS1 3NY, UK. There is extensive evidence indicating the influence of the cholinergic system on emotional responses observed in human and animals. Our previous studies showed that a single systemic injection of a subconvulsant dose of pilocarpine - a non-selective muscarinic receptor agonist – induces an anxiogenic-like profile in rats when evaluated at different behavioral tests of anxiety and time-points (24 h, 1 and 3 months later). In order to better characterize and to shed light on the neural mechanisms mediating the effects induced by pilocarpine, adult male Wistar rats were treated with a subconvulsant dose of pilocarpine (PILO, i.p., 150 mg/kg), re-injected 24 h or 1 month later with GABA-A receptor modulators with anxiolytic (diazepam, DZP, i.p., 1 mg/kg) or anxiogenic (pentylenetetrazole, PTZ, i.p., 15 mg/kg) properties and evaluated in the elevated plus maze (EPM) apparatus. Electroencephalogram (EEG) and biochemical dosages of plasmatic corticosterone (CORT) and ACTH hormones were also performed shortly (24 h) or long-after (1 month) the treatment with pilocarpine. In summary, anxiogenic-like responses were observed when rats were evaluated in the EPM test 24 h or 1 month after PILO, with a decrease in the time spent and number of entries on the open arms of the maze in comparison to control rats (treated with saline). Acute DZP injection blocked the anxiogenic-like effects observed in PILO-treated rats evaluated 24 h or 1 month after the treatment, increasing the time spent and number of entries on the open arms of the maze and risk-assessment behaviors incidence (e.g. unprotected head dipping). On the other hand, the acute injection of PTZ did not alter the behavioral profile of PILO-treated rats evaluated in the EPM test, suggesting the promotion of an anxiogenic top-response observed in this group. No epileptic-like events were observed during EEG recordings after the injection of PILO but an increase of theta activity in the hippocampus, reflecting the cholinergic influence of the septo-hipocampal system over the control of anxiety. Additionally, both CORT and ACTH levels are impressively increased 24 h the injection of PILO whereas only CORT remains elevated 1 month after the treatment, which may suggest the involvement of an epigenetic factor (e.g. glucocorticoids receptors down regulation). Our findings reveal that a single systemic subconvulsant dose of pilocarpine promotes long-lasting effects on the emotional responses of rats, reflected by an increase of anxiogenic-like responses (sensitive to GABA-A signaling), hippocampal theta rhythm activity and anxiety/stress hormonal mediators of rats evaluated 24 h or 1 month after the treatment. In addition, our finding of increased levels of CORT suggests an involvement of hyperactive HPA axis in the anxiety-like effects of PILO. Altogether, these results give support to our previous findings establishing a new research strategy which could be useful as a new tool to model trait anxiety in rats besides highlighting the muscarinic system as a target to future translational studies on this field. Funded by CAPES, CNPq and IBNS grant.

73. **Effect of decabrominated diphenyl ether (BDE-209) exposure during breast milking on the learning and memory function in the CD-1 mice**. Tseng, LH. Department of Environmental Science and Occupational Safety and Hygiene, Tajen University. Ho, YJ. School of Psychology, Chung Shan Medical University. Hsu, PC. Department of Safety, Health and Environmental Engineering, National Kaohsiung First University of Science and Technology. Chang, SH, Graduate Institute of Environmental Management, Tajen University. Decabrominated diphenyl ether (BDE-209), one of the 209 congeners of polybrominated diphenyl ethers (PBDEs), has many applications in products such as electronic enclosures, upholstery textiles and foams. Many researches showed that BDE-209 had already become a new developing environmental pollutant that was recently detected in human milk. PBDEs have been considered as a developmental neurotoxicity that might resulted in behavioral changes following neonatal process. The aim of this study is to assess whether maternal exposure of BDE-209 via breast milking affects learning and memory functions in offspring mice. The pregnant CD-1 mice were randomly divided into control and BDE-209-treated groups. On delivery, the dams were gavaged with BDE-209 at doses of 0 (corn oil), 5, 10, 100 mg/kg BW until the day of weaning. After weaning period, only male mice were kept for further tests. On PND86, three male offspring per litter were selected by random sampling to proceed learning and memory ability tests in Morris water maze. The ability of the mice to find the platform which was located below the surface of the water was tested for 5 consecutive days with 5 trials a day. The test scheme includes learning trail, probe trail and re-learning trail. As far as assessing learning and memory functions were concerned, each

group showed that, after 4 days learning, the time to find the platform was greatly improved. No changes in the percentage of time spent in the target quadrant in the probe trial were found after the platform was removed. Re-learning test also did not show significant difference. No differences in the latency to find the platform were observed in the re-learning in adult offspring mice between BDE-209-treated and control groups, which may indicate neither learning nor memory impairments after maternal exposure to PBDE 209 (0, 10, 100-mg/kg) via breast-milk nursing. This work was funded by the National Science Council of Taiwan under grant NSC101-2410-H-127-001.

74. **Sex differences in impulsive action: Dissociation between systemic and intra-mPFC glutamate antagonism and the effect of amphetamine exposure**. Hammerslag, L. Neuroscience Program, University of Illinois, Urbana-Champaign. Waldman, A. Department of Psychology, University of Illinois, Urbana-Champaign. Aladesuyi Arogundade, O. Department of Psychology, University of Illinois, Urbana-Champaign. Weaver, J. Department of Psychology, University of Illinois, Urbana-Champaign. Gulley, J. Department of Psychology and Neuroscience Program, University of Illinois, Urbana-Champaign. Human drug abusers frequently initiate use during adolescence and are particularly impulsive. The cause of this increased impulsivity is not clear, though one possibility is drug-induced changes in impulse control that result from altered glutamate signaling in the medial prefrontal cortex (mPFC). Here, we used a response inhibition (RI) task to examine the potential role of NMDA receptor function in amphetamine- (AMPH-) induced changes in impulse control. In addition, we tested the extent to which age of exposure and sex contribute to drug-induced changes in impulsivity. Rats were exposed to 3 mg/kg AMPH once every other day (10 injections total) during adolescence (postnatal day (P) 28-45) or adulthood (P85-103). At P120, rats were food restricted and then trained on the RI task, which required them to withhold responding during a signaled 0.5, 1, or 2-s "premature phase" in order to receive a food pellet for a lever press. After behavior stabilized, rats received systemic injections (i.p.) of the NMDA antagonist MK-801 (0-0.08 mg/kg) or AMPH (0-0.9 mg/kg) before each RI session. A separate cohort underwent surgery for implantation of bilateral cannulae directed at the mPFC and were tested on the task before and after local infusion of MK-801 (0-4.0 μg/side). We found that females had better inhibitory control and were more sensitive to systemic MK-801, but less sensitive to intra-mPFC MK-801. Adult exposure to AMPH decreased inhibitory control in females. These results suggest that drug-induced impulsivity develops in an age-and sex-dependent fashion and does not appear to involve changes in NMDA receptor function in the mPFC.

75. **Evidence for altered 5-HT2C receptor function in rats exposed to amphetamine during adolescence or adulthood**. Hankosky, E. University of Illinois, Urbana Champaign, Psychology Dept; Kofsky, N, University of Illinois, Urbana-Champaign, Psychology Dept.; Gulley, J. University of Illinois, Urbana-Champaign, Psychology Dept., Neuroscience Program. Drug use typically begins in adolescence, which is a period of heightened vulnerability due to ongoing neurobiological development. Our lab has shown that amphetamine (AMPH) exposure during adolescence alters orbitofrontal cortex (OFC)-sensitive behaviors, such as behavioral flexibility and reversal learning. Here, we investigated the effects of AMPH exposure on an OFC-sensitive outcome devaluation task. Male and female Sprague-Dawley rats were injected (i.p.) with saline or 3 mg/kg AMPH every other day between postnatal day (P) 27-45 and P85-103. On P125, they were trained twice daily on a Pavlovian conditioning task where a conditioned stimulus (CS; tone or flashing lights) was paired with a specific reward (orange or grape sucrose). Following 10 days of conditioning, one of the two rewards was devalued (via 2 hours of free access) and rats were then given a devaluation test session that consisted of 5 presentations of each stimulus delivered under extinction conditions (i.e. no reward delivery). Twenty minutes prior to the devaluation test, rats were injected with 1 mg/kg SB 242084 (5-HT2C antagonist) or vehicle. Our preliminary data suggest that regardless of sex or age of exposure, rats treated with AMPH continue to exhibit conditioned responses to a CS paired with a devalued outcome. This suggests that the behavior of AMPH-exposed rats is no longer influenced by the value of the reward, but instead is driven by reward-associated cues. Furthermore, in adolescent-exposed rats, pretreatment with SB 242084 reduced responding to a CS paired with a devalued outcome. Overall, our preliminary results suggest that AMPH exposure impairs OFC-sensitive cognitive flexibility and that deficits in 5-HT2C receptor function are a candidate mechanism for this effect.

76. **The role of glycine transmission in the medial preoptic area in regulation of male rats sexual behavior.** Zhuravleva Z.D., Saint Petersburg State University, St. Petersburg, Russia. Number of studies both behavioral and biochemical level show that (Dominguez, et al., 2006; Simerly, 2004) medial preoptic area (MPA) is one of the most important areas of the brain involved in the regulation of sexual behavior in vertebrates (Dominguez , et al., 2006). The role of glycine in the regulation of sexual behavior is still not clear (Malinina, Druzin and Johansson, 2006). The aim of this study was to examine the effect of glycine and strychnine (which is a blocker of glycine receptors) microinjections in the medial preoptic area on sexual behavior of male rats. Registration of males sexual behavior was hold 1) before operational procedures, 2) after the cannulas implantation, and bilateral injections of 2 ml 100 mM glycine, and 3) bilateral injections of 2 ml 0.9% NaCl; 4) repeated bilateral injections of 2 ml 25 mM strychnine. Used concentrations of drugs were also tested on MPO dissociated neurons by «perforated patch-clamp» method. Comparison of the nature of the sexual behavior of males after bilateral microinjection of glycine in the MPA with that of intact males, and after microinjection of saline showed that

glycine significantly increases the number of intromisions and mountings during the first two sessions. Also both glycine and strychnine decrease duration of the first session.

77. **Sex differences in pharmacokinetic of acute administration of methamphetamine in adult Wistar rats.** Šlamberová Romana [1], Bubeníková-Valešová Věra [2], Syslová Kamila [3], Rambousek Lukáš [3], Kačer Petr [3] [1] Charles University in Prague, Third Faculty of Medicine, Department of Normal, Pathological and Clinical Physiology, Prague, Czech Republic. [2] Prague Psychiatric Center, Department of Biochemistry and Brain Pathophysiology, Prague, Czech Republic. [3] Institute of Chemical Technology Prague, Faculty of Chemical Technology, Department of Organic Technology, Prague, Czech Republic. Pharmacokinetic of methamphetamine (MA) was examined in adult male and female rats. Animals were divided into groups based on their scheduled decapitation time (0, 10, 20, 30, 40, 50, 60, 180 min and 6, 9, 12 and 24 hrs post-injection) and administered with a single dose of MA (1 mg/kg or 5mg/kg s.c.). Concentrations of MA and its derivate amphetamine (A) were analyzed by HPLC in plasma and brain of adult male and female rats. The HPLC system was directly coupled to a Varian 1200L triple quadrupole mass spectrometer (Varian, USA) equipped with an electrospray ion source operating in the positive ion mode (ESI^+) for the measurement of A, A-d_5, MA, MA-d_5. Area under the plasma and brain concentrations versus time curve (AUC) values was calculated for the averaged data with the log-trapezoidal rule from time zero to the last experimental data point (0-24h). Our results demonstrated that the highest MA concentrations were achieved after 60 min in both plasma and brain without effect of sex. Calculated plasmatic AUC values for MA in male rats were higher (28% higher after 1mg/kg, 24% higher after 5mg/kg) than for female rats. AUC values for brain levels were increased as well in male rats compared to female rats (19% higher after 1mg/kg, 16 % higher after 5mg/kg). On the other hand plasmatic AUC values for A in male rats were lower (17 % lower after 1 mg/kg, 11 % lower after 5 mg/kg) than for female rats but there were only slight differences in brain AUC values (1 % lower after 1 mg/kg, 4 % lower after 5 mg/kg). Thus, our data demonstrate that there are sex differences in the MA and A concentrations in the blood and brain of adult rats that may explain the sex-dimorphic effect of MA on behavior in these animals. Supported by: GACR P303/10/0580, PRVOUK P34

78. **Facilitation of 2-arachidonoylglycerol (2ag) signaling in the dorsolateral periaqueductal gray in rats induced anxiolytic-like effects**. 1Gobira, PH. 1Almeida-Santos, AF. 1Moreira, FA. 1Aguiar, DC. 1Pharmacology Department, ICB-UFMG. Introduction: Anandamide and 2-araquidonoilglicerol (2AG) are the main representatives of the endocannabinoid system. Anxiolytic-like effects were described for anandamide in different animal models of anxiety, such as the elevated plus maze (EPM). These effects are mediated through activation of cannabinoid receptors type 1 (CB1r), which are highly expressed in several brain regions related to defensive behavior, such as the periaqueductal gray (PAG). However, the role of 2AG in behavioral responses mediated by the dlPAG is not yet described. Thus the objective of this study was to test the hypothesis that the administration intra-dlPAG of the 2AG or increase endogenous levels of 2AG, by inhibiting monoacylgycerol lipase (MAGL), will exert anxiolytic-like effects in animals submitted to the EPM. The mechanism involved in this behavioral response was also investigated. Methods: Male Wistar (n= 5-12/group) with cannula aimed at the dlPAG received injections (0.2 μL) of the following treatments: Experiment 1: vehicle (veh) or 2AG (5pmol, 50pmol, 500pmol). Experiment 2: veh or URB602 (MAGL inhibitor, 30pmol, 100pmol or 300 pmol). Experiment 3: veh or AM251 (antagonist CB1r, 100pmol) followed 10 minutes later by injection of veh or 2AG Experiment 4: veh or AM630 (antagonist CB2r, 1000pmol) followed 10 minutes later by injection of veh or 2AG (50pmol). The animals were exposed to EPM ten minutes after the last injection for 5 minutes. Results: The administration of 2AG (50pmol) significantly increased the number of entries in the open arms of the EPM (veh: 11.52 ± 4.72; 2AG (50pmol): 37.65 ± 3.71, $F(3,33) = 4.2$, $p = 0.01$; Duncan, $p < 0.05$ compared to vehicle group), suggesting an anxiolytic-like effect. Likewise, the intra-dlPAG injection of URB602 (100pmol) induced a significant increase in time spent in the open arms of the EPM (veh: 9.01 ± 3.20; URB602 (100pmol): 30.71 ± 6.86, $F(3,26) = 1.2$, $p = 0.1$; Duncan, $p < 0.05$ compared to vehicle group). Both pretreatment with AM251 and AM630 attenuated the anxiolytic-like effect induced by 2AG. However, the effects of MAGL inhibitor were blocked only by CB2 antagonist. Discussion: Our results showed that the augmentation of 2AG signaling induce anxiolytic-like effects. But these effects were mainly related trough CB2 activation, since the effects of MAGL inhibitor were blocked by CB2 antagonist but not by CB1 antagonist.

79. **The facilitating effects of testosterone-sildenafil co-treatment on sexual behavior in female rats depend on the delayed effects of testosterone.** Elisabeth Y Bijlsma[1], Marin Jonker[1], Jos Bloemers[1,2], Adriaan Tuiten[1,2], Berend Olivier[1], Ronald Oosting[1] [1] Department of Pharmacology. Utrecht Institute for Pharmaceutical Sciences and Rudolf Magnus Institute of Neuroscience, Utrecht University, Utrecht, the Netherlands [2] Emotional Brain B.V., Almere, The Netherlands. Hypoactive sexual desire disorder (HSDD) is a common problem in women and decreases their quality of life. In women with HSDD, co-treatment of sublingually-administered cyclodextrine-bound testosterone and vardenafil (phosphodiesterase 5 inhibitor) shows beneficial effects of on sexual desire under laboratory conditions [Van der Made et al 2009]. Interestingly, the clinical study indicated a time laps between the pharmacokinetic profile of T and subsequent facilitating effects. That is, plasma levels of T peak within 15 minutes and return to baseline levels within 2 hrs, whereas facilitation of sexual desire only becomes apparent after about 4 hrs. We recently showed that co-treatment of vardenafil and testosterone propionate (TP,

administered 4 hrs before testing) also facilitates sexual behavior in hormonally sub-primed female rats [Snoeren et al 2011]. The current study was employed to study whether above mentioned time laps in the behavioral effects of TP during co-treatment is also crucial for the facilitating effects in sub-primed female rats. Ovariectomized female rats, sub-primed with only estradiol, were tested in a paced-mating sex test. Proceptive (darting and hopping), receptive (lordosis score and lordosis quotient) and paced mating (percentage exits and contact-return latencies) behaviors were quantified following co-treatment of TP and Sildenafil. TP (300µg, s.c.) was administered 1 or 4 hrs before the paced mating test and was given alone or in combination with sildenafil (3 or 10 mg/kg, p.o.). Treatment with TP at -4 hrs in combination with sildenafil caused a significant increase (~1.4 fold) in proceptive behavior in sub-primed rats. TP administration at -1 hr in combination with sildenafil, however, had no effect on sexual activity. We conclude that co-treatment of TP and sildenafil increase sexual activity in a time-dependent manner. The delay in behavioral effects observed, suggest that genomic effects of testosterone-induced androgen receptor activation play a substantial role in the facilitating effects of TP and sildenafil co-treatment.

80. **Amphetamine exposure during adolescence alters dopaminergic modulation of inhibitory transmission in the medial prefrontal cortex**. S. Kang, K. Paul,C.L. Cox, and J.M. Gulley; Dept. of Psychology and Program in Neuroscience, Champaign, IL, USA. Repeated exposure to amphetamine (AMPH) has been suggested to induce adaptive changes in dopamine receptor function in the prefrontal cortex (PFC). Since dopamine plays an important role in regulating GABAergic transmission in the PFC, the current study sought to determine whether chronic amphetamine exposure during adolescence would alter dopamine's modulation of inhibitory transmission in layer V pyramidal cells of the PFC. Male Sprague-Dawley rats were given saline or 3 mg/kg AMPH (i.p.) every other day from postnatal day 27 to 45. Thirty days later, we used whole-cell patch recordings to measure spontaneous inhibitory postsynaptic currents (sIPSCs) and their potential modulation by bath application of amphetamine (25 µM) and manipulation of dopamine D1 and D2 receptors. We found no group differences in the amplitude or frequency of sIPSCs during baseline recording. Following the application of amphetamine, there was a significant increase in sIPSCs frequency in cells recorded from controls. In contrast, there was a significant decrease in amphetamine pre-exposed rats that was partially reversed by sulpiride (5 µM), suggesting an enhanced D2 function induced by amphetamine pre-exposure. We also found that after bath application of the selective D1 agonist SKF38393 (10 µM), sIPSC frequency in amphetamine-exposed rats was significantly lower than that in controls, suggesting an impairment in D1 function. Taken together, these results suggest that exposure to amphetamine during adolescence could have an enduring disruptive effect on dopamine's modulation of inhibitory transmission in deep layer PFC. The altered inhibitory modulation could be attributed to a heightened D2 function and reduced D1 function in pre-exposed rats.

81. **Sex differences in central amygdala GABAergic neuron density and anti-anxiety efficacy of diazepam in outbred lines of high and low anxiety Long Evans rats.** Donaldson, S.T.[1]; Ravenelle, R.[2]; Niedzielak, T.[3] [1]Developmental Brain Sciences, Psychology Department, University of Massachusetts Boston, Boston, MA 02125; [2]Department of Biological Sciences, Fordham University, Rose Hill Campus, Bronx, NY 10458; [3]College of Osteopathic Medicine, Nova Southeastern University, 3301 College Avenue, Fort Lauderdale-Davie, Florida 33314. Animal models of trait anxiety are often used to explore the neurobiological mechanisms underlying pathological anxiety. Benzodiazepines, such as diazepam (DZ) have long been used to treat anxiety disorders with mixed results. We set out to evaluate any sex and neural contributions to the anti-anxiety efficacy of DZ. Adult male and intact female Long Evans rats from preexisting high (HAn) and low (LAn) anxiety lines were tested in the elevated plus maze (EPM) for baseline and post-DZ (30 min after 1mg/kg IP) to determine if pre-existing anxiety traits and/or sex would affect anxiety-like behavior (ALB). Immunocytochemistry was performed on 30µm sections of the central amygdala (CeA) and dorsal striatum (CPu) to detect the number of GABAergic cells (anti-parvalbumin), a major target of DZ. At baseline, HAn rats showed greater ALB, fewer OA entries and percent OA time, regardless of sex. Following acute DZ, this was reversed for males who showed an increase in %OA time as indicated by a significant Trait x DZ interaction. Intact females had significantly more GABAergic cells in the CPu than males regardless of trait, however, there was a Trait x Sex interaction with LAn females exhibiting more GABAergic cells than those classified as HAn. Males showed an increased number of GABAergic cells compared to females in the CeA. Taken together, these data suggest that anxiety-like behavior and central amygdala GABA cell density may vary by sex in trait anxiety animals to influence the anti-anxiety effects of acute diazepam.

82. **Ethanol induced motor impairment involves inhibition of α7 nAChRs**. Wolfman, S.L. University of Chicago Committee on Neurobiology. McDaid, J. University of Chicago Department of Anesthesia and Critical Care. Gallagher, K. University of Chicago Department of Anesthesia and Critical Care. McGehee, D.S. University of Chicago Department of Anesthesia and Critical Care and Committee on Neurobiology. Nicotine and ethanol (EtOH) are two widely co-abused drugs. EtOH impairs motor activity and has rewarding effects. The stimulant effects of nicotine might offset this motor impairment, but the mechanisms underlying these interactions remain unclear. A major challenge in understanding the behavioral effects of EtOH is the identification of molecular targets that mediate those behaviors. EtOH has been shown to modulate nicotinic acetylcholine receptors (nAChRs) in cell culture, but no such studies have been done in brain slices. To investigate this interaction, we

tested the effect of bath applied EtOH on nAChR-mediated currents using slice electrophysiology in the lateral dorsal tegmentum (LDTg) of adult rats. The LDTg contributes to motor performance and reward circuitry. Most nAChR responses in LDTg neurons were completely blocked by the selective α7* antagonist MLA (10 nM). Bath application of EtOH at physiologically relevant levels (1-10mM) profoundly reduced the magnitude of the α7* nAChR responses. This inhibitory effect was blocked by either intracellular H89 (PKA inhibitor) or SQ22536 (AC inhibitor). Bath application of the α7* nAChR positive allosteric modulator PNU120596, which interferes with α7* nAChR desensitization, eliminated the effects of EtOH on α7* nAChRs. Also, phosphorylation state of α7* nAChRs in the LDTg was decreased after EtOH administration. Thus, EtOH inhibits α7* nAChRs by enhancing desensitization via the PKA pathway. Additionally, we found that intra-cerebroventricular injection of PNU120596, which reduces EtOH-induced inhibition of α7* nAChRs, also reduced EtOH-induced motor impairment in rats. These findings suggest that motor impairment by EtOH is mediated, at least partially, by a reduction in α7* nAChR-mediated excitation. Future directions will examine a role for this interaction in nicotine reward.

83. **Participation of the Serotonin and Angiotensin-(1-7) in behavioral responses in transgenic rats with low brain angiotensinogen.** Almeida-Santos, A.F.[1]; Kangussu, L.M.[2]; Campagnole-Santos, M.J.[2]; Aguiar, D.C[1]. [1]Pharmacology Department. [2]Physiology and Biophysics Department. Biological Science Institute, Federal University of Minas Gerais. Brazil. Introduction: The transgenic rat with low brain angiotensinogen - TGR(ASrAOGEN) 680, characterized by a transgene-producing antisense RNA against angiotensinogen in the brain, provides an opportunity to study the behavioral effects of angiotensin. Previous work described an anxious phenotype in TGR(ASrAOGEN)680 rats and a low tissue content of 5-HT in the hippocampus and frontal cortex. The objective of this study was to investigate the participation of the 5-HT and the Angiotensin-(1-7) in anxiety responses of TGR(ASrAOGEN)680 rats. Methods: Exp 1: Male adults ASrAOGEN680 and Sprague-Dawley (SD) rats received i.p. injections of vehicle or fluoxetine (10 mg/kg) and and 60 min later were exposed to the Elevated Plus Maze (EPM). Exp 2: TGR(ASrAOGEN)680 and SD rats with cannulae aimed at the in right lateral brain ventricle (AP: -1 mm, L-1,6 mm, P-4,0 mm) received i.c.v injections of vehicle (1.0 μL) or Ang-(1-7) (1μmol/1.0 μL) and 10 min later were exposed to the EPM. Results: Exp 1: Fluoxetine (10mg/kg) was able significantly to revert the lower in the percentage of entries into the open arms of EPM in TGR(ASrAOGEN)680, but fluoxetine not promote any behavioral alteration in SD rats. Exp 2: Ang-(1-7) (1μmol/1.0 μL) administered into right lateral ventricle was able significantly to revert the lower in the percentage of entries and percentage of time into the open arms of EPM in TGR(ASrAOGEN)680 rats, but Ang-(1-7) (1μmol/1.0 μL) not promote any behavioral alteration in SD rats. Neither Ang-(1-7) nor fluoxetine were able to promote alteration in locomotor activity. Data were analyzed by Two-Way ANOVA. Conclusion: The results suggest an anxious phenotype in TGR(ASrAOGEN) 680 rats is reversed by administration of fluoxetine and Angiotensin-(1-7). Financial support: CAPES/ FAPEMIG/ CNPQ

84. **Regulation of arc through miR-495 as a potential mediator of cocaine motivation and extinction learning**. Bastle, R.[1]; Pentkowski, N.[1]; Turk, M.[1]; Adams, M.[1]; Berger, A.[1]; Dado, N.[1]; Smith, K.[1]; Hammer, R.[2]; Perrone-Bizzozero, N.[3]; Neisewander, J.[1] [1]Arizona State University. [2]University of Arizona-College of Medicine. [3]University of New Mexico. MicroRNAs are small, non-coding transcripts that regulate gene expression post-transcriptionally and recently have been implicated in drug addiction. We found that the microRNA, miR-495, is downregulated in the nucleus accumbens (NAc) following acute cocaine administration whereas one of its predicted target mRNAs, that for the activity-regulated cytoskeleton associated protein (arc), is upregulated. Using a lentiviral vector (LV-miR-495) to increase miR-495 expression in the NAc shell (NAcsh) in drug naïve rats, we found an increase in miR-495 and a corresponding decrease in arc expression compared to LV-GFP controls, suggesting that arc mRNA is regulated by miR-495 in vivo. We then tested the functional role of miR-495 in regulating arc and cocaine self-administration. Rats were trained to self-administer cocaine (0.75 mg/kg/0.1 ml) on a fixed ratio (FR) 5 schedule of reinforcement and after stable responding on a within-session dose-response function (0, 0.1, 0.3, 1.0 mg/kg; FR5), we infused either LV-miR-495 or LV-GFP into the NAcsh. Four days later we tested rats on the dose-response function and the following day on a progressive ratio (PR) schedule of reinforcement. LV-miR-495 did not alter the dose-response function for cocaine intake on an FR5, but did significantly decrease intake and response rates on the PR compared to controls, suggesting miR-495 may regulate cocaine motivation, rather than reinforcement per se. We are currently measuring RNA levels of arc and miR-495 across extinction of cocaine seeking when motivation varies across time in order to determine whether miR-495 has a regulatory role over arc and cocaine seeking. Thus far, the results suggest that miR-495 regulates gene expression associated with motivation for cocaine. Supported by DA034097 and DA025992

85. **Repeated administration of cannabidiol induces an anxiolytic-like effect in mice submitted to chronic unpredictable stress by facilitation of endocannabinoid neurotransmission**. Fogaça, MV; Guimarães, FS / School of Medicine of Ribeirão Preto, University of São Paulo (USP), Ribeirão Preto, São Paulo, Brazil. Chronic stress induces neuroplastic and behavioral changes that can lead to the development of anxiety disorders. Previous studies of our group indicated that repeated injection of cannabidiol (CBD), a non-psychotomimetic cannabinoid present in the Cannabis sativa plant, attenuates the anxiogenic-like effect induced by chronic unpredictable stress

(CUS). An in vitro study also suggested that CBD effects depend on facilitation of endocannabinoid-mediated neurotransmission by inhibition of the fatty acid amide hydrolase (FAAH) enzyme. The aim of this study was to investigate if the behavioral effects induced by repeated administration of CBD in mice submitted to CUS are mediated by the endocannabinoid system. C57BL6/J mice were divided in non-stressed and stressed groups. Stressed animals were submitted to CUS during two weeks, being exposed to different randomized stressors each day. One hour after the daily stressor the animals received combined injections of vehicle, the CB1 receptor antagonist AM251 (0.3 or 1,0 mg/kg), and/or CBD (30 mg/kg). On day 14, approximately 24 h after the last injection, the animals were tested in the elevated plus maze (EPM) and on day 15 the animals were submitted to the novelty suppressed feeding test (NSF). The hippocampus was extracted to perform Western Blot analysis of FAAH expression. Results were analyzed by one- or two-way ANOVA and Student's t or Duncan test. Stressed mice presented a decreased exploration of the EPM open arms and increased latency to feed in the NSF test, an anxiogenic-like effect. These effects were prevented by CBD chronic treatment. In both models, the anxiolytic-like effects of CBD were attenuated by pretreatment with AM251. Moreover, CBD decreased FAAH expression only in stressed mice, which was not attenuated by AM251. These results suggest that CBD prevents the behavioral effects of CUS by facilitating endocannabinoid-mediated neurotransmission and CB1 receptor activation. Financial support: FAPESP, CAPES

86. **Effects of fluoxetine in corticosterone-induced depressive-like phenotypes in postpartum and nulliparous females**. Joanna L. Workman, Nicole F. Kitay, Carmen Chow, Liisa A.M. Galea. Department of Psychology and the Centre for Brain Health, Vancouver, Canada. Women are 2 - 3 times more likely than men to suffer from depression and the greatest risk for a depressive episode is during the postpartum period, which not only negatively affects the women who suffer, but can also negatively impact child development. Considerable evidence links stress, and in particular the stress hormone cortisol, with depression. On average, individuals with depression have higher cortisol concentrations and an impairment HPA negative feedback. Indeed, in many animal studies, chronic variable stressors or exogenous corticosterone (CORT; the primary glucocorticoid in rats) induce a depressive-like behavioral and neural phenotype. However, most models of depression have primarily used males. Prior research from our laboratory has established that administering high CORT to females during the postpartum period leads to reduced maternal care, depression-like behaviour, reduced hippocampal neurogenesis and CA3 pyramidal cell complexity. Collectively, this suggests that CORT induces a depressive-like phenotype in postpartum rats. However, it is currently unknown whether the postpartum period yields greater susceptibility to high stress hormones and whether this phenotype can be reversed. Thus, the goals of this study were first, to understand how CORT alters behavior and the brain in females at different reproductive time points and second, to determine if a CORT-induced behavioral phenotype can be reversed using a commonly prescribed antidepressant (including for women with postpartum depression), fluoxetine (FLX). Female Sprague Dawley rats were randomly assigned to either be mated or remain reproductively inexperienced (nulliparous). Then, rats were subsequently assigned to receive either CORT or oil and FLX or saline, yielding 8 groups. All rats were given CORT/oil and FLX/saline concurrently every day for 22 days (for rats in the postpartum condition, this coincided with the postpartum days 1 – 23). Maternal care was observed from postpartum days 1 – 8 and depressive-like behaviors were assessed in the forced swim test (FST) on days 22 and 23. As previously established, CORT disrupted maternal care. Further, CORT significantly increased immobility in the FST in both postpartum and nulliparous rats. Finally, FLX reversed some aspects of the depressive-like phenotype. Notably, FLX fully reversed CORT-induced changes in maternal care, suggesting that some antidepressant effects of fluoxetine may occur earlier than previously thought. We are currently investigating how CORT and FLX regulate neurogenesis and other forms of hippocampal plasticity. These data will contribute to our understanding of how reproductive states may alter the susceptibility to depression and antidepressant efficacy.

87. **The effects of calorie restriction on fever and neuroimmune communication pathways in mice.** Radler, M., Smith, G., Hale, M.W, Kent, S. School of Psychological Science, La Trobe University, Melbourne, VIC, Australia. Calorie restriction (CR) has been shown to increase longevity and elicit many health promoting benefits, including delaying the development of diabetes, improving learning and memory, and reducing anxiety. In addition, CR has been shown to attenuate fever and sickness behaviour in response to systemic immune challenges. However, it is unclear how the neuroimmune pathways that relay immune signals between the brain and the periphery are affected by CR. The current study examined the expression of c-Fos, the protein product of the immediate early gene (IEG) c-fos, in brain regions known to be involved in neuroimmune communication pathways. Twenty-two male C57BL-6J mice were either fed ad libitum or were subjected to a CR dietary regimen for four weeks. Following the CR period, mice were injected with saline or 50 μg/kg of lipopolysacharide from Escherichia coli (serotype 0111:B4). Immunohistochemistry was conducted and cells that expressed c-Fos were counted in five regions of the medulla and pons, including the lateral parabrachial nucleus, locus coeruleus, nucleus of the solitary tract and the area postrema. Lipopolysaccharide increased c-Fos expression; however, CR did not alter c-Fos expression in the regions examined. This indicates that CR attenuation of fever and sickness behaviour does not occur peripherally, but is instead moderated by central mechanisms. Neuroinflammation was also examined as a possible mechanism and data will be presented at the meeting.

88. **Fos expression after exposure to social and nicotine rewards or reward-conditioned environments in adolescent male rats**. Peartree, N.A., Williams, A.M., Bastle, R.M., Goenaga, J., Chandler, K.N., Hood, L.E., Neisewander, J.L. Arizona State University. Tempe, AZ, USA. Adolescence is a period of enhanced sensitivity to social and drug rewards. We have shown that nicotine and social reward interact to produce greater conditioned place preference (CPP) in adolescent rats than either stimulus alone. Our aim was to investigate the neural processing underlying the combination of social and nicotine rewards within the Nucleus Accumbens Core (NAcC) and Shell (NAcSh), Medial (MeA), Central (CeA) and Basolateral Amygdala (BLA), Anterior Cingulate Cortex (Cg1) and the Ventral Tegmental Area (VTA). Adolescent male Sprague-Dawley rats were assigned to groups that either received saline (Sal) or nicotine (Nic; 0.1 mg/kg/mL SC) and were then immediately placed into their conditioning apparatus either alone (Iso) or with a partner (Soc), resulting in 4 groups: 1) Nic+Soc; 2) Nic+Iso; 3) Sal+Soc; or 4) Sal+Iso. Brains were harvested for Fos protein immunohistochemistry either after their final conditioning session with their reward(s) or after a final place preference expression test, in which rats were given access to both sides of the apparatus without any drug treatment or social exposure. We found that all groups exhibited a preference switch of more than 50% of the total test time spent in their reward-paired side, except for the Sal + Iso controls. Social reward conditioning attenuated NAcC activation during expression of CPP. In contrast, experiencing social reward itself during conditioning increases activation of the MeA, CeA, NAcC, and NAcSh. Rats that experienced nicotine during conditioning displayed decreases activation of the NAc Core and Cg1. Experiencing both nicotine and social rewards produced greater activation of the BLA and VTA relative to nicotine or social rewards alone, respectively. The findings are further complicated by activation of BLA and VTA in controls, suggesting a potential isolation stress effect. Supported by DA023123, DA023746, DA11064, and F31DA033805.

89. **Effects of harmane on prepulse inhibition in rats**. Kayir, H. Gulhane Medical School, Ankara, Turkey. Kilicarslan, I. Ege University, Faculty of Pharmacy, Izmir, Turkey. Kara, A. Gulhane Medical School, Ankara, Turkey. Calik, M. Gulhane Medical School, Ankara, Turkey. Goktalay, G. Uludag University, Department of Medical Pharmacology, Bursa, Turkey. Uzbay, T. Gulhane Medical School, Ankara, Turkey. Beta-carboline harmane targets imidazoline, glutamatergic, and monoaminergic pathways may involve the brain pathways mediating sensorimotor gating. We tested the effects of harmane on prepulse inhibition of the acoustic startle reflex (PPI), which is a measure of sensorimotor gating and an animal model for screening antipsychotic activity. Adult male Wistar rats were subjects. PPI was measured as the percent inhibition of the startle reflex produced by a startling pulse in presence of prepulse stimuli. The average PPI levels were used in the further analyses. Harman or its vehicle (1% acetic acid) i.p. injected 30 min prior to MK801 or apomorphine or their vehicles. Harmane treatment had no effect on PPI [$F(4,34)=0.906$; $p>0.05$] at the selected dose range (2.5–20 mg/kg). MK801 (0.15 mg/kg) disrupted PPI ($p<0.05$) without altering the startle reflex ($p>0.05$). Harmane (2.5–20 mg/kg) pretreatment had a significant effect on MK801 induced disruption of PPI [$F(4,32)=7.921$; $p<0.0001$]. Post-hoc Dunnett's test revealed that harmane 2.5 mg/kg prevented the MK801 induced PPI disruption ($p<0.05$). However at the doses higher than 5 mg/kg, observed preventive effect disappeared and harmane 20 mg/kg tended to augment MK801 induced PPI disruption. Apomorphine (2 mg/kg) disrupted PPI ($p<0.01$) and increased startle reflex ($p< 0.01$). Harmane (5-20 mg/kg) did not have any effect on apomorphine induced PPI disruption [$F(3,30)= 1.541$; $p> 0.05$], but reversed the increase of startle reflex [$F(3,30)=6.765$; $p< 0.001$] at all the doses used (p values< 0.05). Our results suggest that harmane has no effect on PPI, but modulates the MK801 induced disruption in a biphasic manner. Harmane reverses the effect of MK801 at a low dose while augments it at a higher dose. It has no effects on apomorphine induced PPI disruption. In conclusion, harmane may have a modulatory role in disorders with sensorimotor gating deficits through NMDA rather than dopaminergic receptors. Supported by TUBITAK (110S344).

90. **Not presented.**

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91. **Participation of NK1 receptors of the amygdala on the processing of different types of fear.** Carvalho, M.C.1,2; Santos, J.M.1,2; Brandão, M.L.1,2 Instituto de Neurociências e Comportamento, Campus USP, Ribeirão Preto, SP, Brasil1; Laboratório de Neuropsicofarmacologia, Faculdade de Filosofia, Ciências e Letras, Universidade de São Paulo, Ribeirão Preto, SP, Brasil2. The amygdala (AM) together with the dorsal periaqueductal gray (dPAG) has been considered the main neural substrate for the integration of unconditioned aversive behavioral states. The basolateral nucleus (BLA) is thought to act as a filter for innate and learned aversive information to higher structures, whereas the central nucleus (CeA) is considered the main output for the expression of fear reactions through projections to limbic and brainstem regions. Although neurokinin (NK) receptors are abundant in the AM, their role in the processing and expression of fear is unclear. So, we examined the role of SP/NK1 receptor system of the CeA and BLA on the expression of defensive responses of Wistar rats submitted to elevated plus maze (EPM) and to electrical stimulation (ES) of the dPAG. For EPM test, cannulae were implanted in the CeA or BLA for injections of substance P (SP) and spantide (SPA). For ES of dPAG, aversive thresholds for freezing and escape responses as well as post-stimulation freezing (PSF) were measured in rats treated with PBS and SPA in CeA. Injections of SP only in the CeA produced anxiogenic-like effects in the EPM and SPA was able to inhibit them. But, SPA per se had no effects. Interestingly, the duration of dPAG-PSF was reduced significantly following injection of SPA in CeA but had no effect on thresholds for freezing and escape responses. The EPM gives the rat a control over its environment i.e. the option to choose or not to enter into the open arm and dPAG-PSF is thought to reflect a period when the rat evaluates the significance of dPAG-evoked aversion once the unconditioned responses of freezing and escape were elicited. The data indicate that SP may be involved in mediating responses of the rat in only certain types of aversive behavior and suggests a differential participation of the NK1 receptors in the processing of distinct types of fear in the AM.

92. **Effects of fluoxetine exposure during adolescence on cocaine CPP in adulthood.** Nieto, S.[1]; Riggs, L.[1]; Dayrit, G.[1]; Cao, V.[1]; Zamora, N.[1]; Rodriguez, R.[1]; Warren, B.[1] and Iñiguez, S.[1] [1]Department of Psychology, California State University, San Bernardino, CA 92407. Pediatric depression was almost unthinkable until several years ago. Now we not only know that major depressive disorder (MDD) exists in children and adolescents, but that it is also a common condition. It is estimated that children and adolescents who suffer from MDD often develop conduct and anxiety disorders, and that 20-25% develop substance abuse disorder. Consequently, this has resulted in a disproportionate increase in the prevalence of antidepressants prescribed to populations below 20 years of age. Despite the heightened rates in antidepressant use, little is known about the long-term behavioral adaptations resulting from antidepressant treatment during periods before adulthood. To address this problem, at the preclinical level, we examined if fluoxetine (Prozac) exposure during adolescence results in long-lasting changes to the rewarding effects of cocaine (0, 2.5, 5, 10, or 20 mg/kg). Specifically, male C57BL/6 mice were exposed to Prozac (20 mg/kg) during adolescence (postnatal days 35-49) and were later assessed in adulthood (postnatal day 70+) on behavioral responsivity to cocaine place conditioning (CPP). Our results show that Prozac pre-treated animals displayed an enhanced preference for environments previously paired with cocaine (5 or 10 mg/kg), when compared to saline pre-treated controls. Thus, our findings suggest that adolescent Prozac exposure increases sensitive to the rewarding effects of cocaine later in life, as inferred from the CPP paradigm.

93. **Relapse to methamphetamine-seeking behaviour is reduced by oxytocin administration in the nucleus accumbens core of the rat**. Baracz, S.J.[1]; Everett, N.A.[1]; McGregor, I.S. [2]; Cornish, J.L [1] [1] Macquarie University, North Ryde, Australia; [2] University of Sydney, Sydney, Australia. The psychostimulant methamphetamine (METH) is an addictive illicit drug of abuse. The neuropeptide oxytocin has been identified as a modulator of METH-related reward and METH-seeking behaviour, however little is known about the neurobiological mechanisms involved. Recent findings have implicated the nucleus accumbens core (NAc core) as a key substrate involved in oxytocin modulation of acute METH-induced reward. It is not known, however, if oxytocin acts in this region to reduce relapse to METH-seeking behaviour. We aimed to investigate the effect of a pretreatment of oxytocin within the NAc core on relapse to METH use utilising a reinstatement model of drug seeking behaviour. Male Sprague Dawley rats underwent surgery to implant an intravenous jugular vein catheter and bilateral microinjection cannulae in the NAc core under isoflourane anaesthesia. After a recovery period of 5-7 days, rats were trained to self-administer intravenous methamphetamine (0.1 mg/kg/infusion) by lever press during 2 hour sessions under a fixed ratio 1 schedule for 20 days. Following extinction of lever press activity, METH-induced (1mg/kg, i.p.) reinstatement of responding at the drug-paired lever was examined following treatment with an intracranial infusion of oxytocin (0, 0.2ng, 0.6ng, 1.8ng/side) in the NAc core (500 nl/side). On the final reinstatement day, rats were tested with a microinjection of the highest oxytocin dose prior to a saline i.p. injection. Our results showed that oxytocin administration to the NAc core decreased METH-induced reinstatement in a dose dependent manner, with significant reductions produced by 0.6 and 1.8 ng/side of oxytocin. These findings further demonstrate that oxytocin is an important mediator of METH abuse and that this effect of oxytocin is produced at the level of the NAc core.

94. **Lateral habenula lesions reduce the anxiogenic response to self-administered cocaine**. Shelton, K.1; Wenzel, J.1; Sved, S.1; Ettenberg, A.1 1 University of California, Santa Barbara, California USA. The Opponent Process Theory of motivated behavior postulates that all affective stimuli produce diametrically opposite and temporally dissociated actions. Thus a rewarding incentive stimulus would be expected to produce a delayed counter-reaction (opponent process) intended to return the organism to affective homeostasis. Our laboratory has reported that self-administered cocaine produces behavioral effects consistent with opponent-process theory – an initial euphoric reaction followed by an anxiogenic/anhedonic "crash". While the positive motivating effects of cocaine agonists have long been thought to require an intact mesolimbic dopamine (DA) system, the neural mechanisms that give rise to the negative effects of the drug remain less clearly defined. Recent literature points to the lateral habenula (LHb) as a site for the encoding of aversive events and to "gate" the activity of the DA reward system by inhibiting the activity of DA cells within the VTA. The current study investigated the role of the LHb in modulating the aversive/anxiogenic properties of cocaine as measured in a runway model of IV self-administration. Male rats were stereotaxically administered bilateral kainic acid lesions of the LHb and then trained to run a straight alley for IV cocaine (1.0 mg/kg) delivered upon goal-box entry. Over trials, sham-lesioned animals developed retreat behaviors in which rats rapidly approached, but then stopped and retreated away from the cocaine-associated goal box. In contrast, lesions of the LHb significantly diminished the occurrence of this cocaine-induced approach-avoidance conflict. Such results suggests a role for the LHb in the aversive/anxiogenic effects of cocaine. This work was supported by grants DA05041 and DA033370 awarded to AE.

95. **The anabolic steroid, 17α-methyltestosterone, accelerates the transition from rough and tumble play towards sexual-related behaviors**. 1Silva-Gotay A., 2Ramos-Pratts K., 2Barreto-Estrada, J.L. 1Department of Chemistry, University of Puerto Rico, Río Piedras Campus, San Juan, PR 00936, 2Department of Anatomy and Neurobiology, Medical Sciences Campus, University of Puerto Rico, San Juan, PR 00936. Rough-and-tumble play emerges shortly after weaning and depends upon differential exposure to testosterone during the perinatal period. Reaching adulthood, rough-and-tumble play starts to decline and is replaced by motivational and consummatory components of sexual behavior. Most studies show that deprivation of androgens attenuates social play. However, there is no research on how supraphysiological doses of synthetic androgens affect this behavior. In this study we aim to assess the effect of the anabolic androgenic steroid (AAS), 17α-methyltestosterone (17α-meT) in the development of rough-and-tumble play into sexual behavior. We expect that such exposure will decrease rough and tumble, accelerating the development of mature sexual competence. Juvenile male rats (PN-28), received daily injections of 17α-meT (7.5 mg/kg), and play was observed at two different time points: at PN-35 and at PN-45. Parameters scored were pouncing, pinning, boxing, wrestling, and mountings. In the absence of AAS, pinning was more frequent at PN-35, while pouncing and mounts showed higher frequencies at PN-45. Daily 17α-meT injections from PN-28 to PN-35 significantly decreased pinning and wrestling, whereas a tendency to increase the frequency of mounts was observed. Daily 17α-meT injections from PN-28 to PN-45 revealed tendencies to decrease pouncing and to increase mounts. Our results suggest that early AAS exposure decreases rough and tumble play and sets forward the transition to a more mature sexual behavior. NIH-NIGMS (5R25GM097635-02 and 8P20GM103475-12).

96. **The potential role of neurexins and neuroligins in the pharmacological and behavioral effects of nicotine**. Bernardi, R.E., Uhrig, S., Spanagel, R., Hansson, A.C. Institute of Psychopharmacology at the Central Institute of Mental Health, Medical Faculty Mannheim / University of Heidelberg. Neurexins and Neuroligins are neural cell adhesion molecules that induce synapse formation and modulate synaptic activity, best known for their potential role in disorders such as autism. Recent studies in animals and humans have suggested that these molecules may play an important role in many functions, such as learning and memory, and may be involved in drug dependence. The purpose of this study was to determine the potential role of neurexins and neuroligins in the neuroadaptations involved in nicotine exposure. Using quantitative in situ hybridization with subtype-specific riboprobes, we examined expression levels of Neurexins 1-3 and Neuroligins 1-3 in reward-related forebrain regions of mice treated with chronic nicotine or saline for 14d (0.175 mg/kg, IP) and sacrificed 1d or 7d following the last injection. A further group mice received a single nicotine injection (0.175 mg/kg, IP) and were sacrificed 1d later. The data strongly suggest the differential involvement of Neurexins 1-3 and Neuroligins 1-3 in nicotine-related processes. Using these in situ data, we identified gene candidates in specific brain areas most likely to affect behaviors associated with nicotine intake for reverse genetic approaches using gene silencing. For example, we found that Neuroligin 1 (NLGN1) was upregulated in the nucleus accumbens (NAcc) shell during early exposure to nicotine. Thus, in an initial study, lentiviral-mediated siRNA for NLGN1 was microinjected into the NAcc shell of rats prior to nicotine self-administration. NLGN1 knockdown produced an alteration in nicotine self-administration as compared to controls, suggesting the involvement of NLGN1 in nicotine-mediated behaviors.

97. **Effects of anxiolytic and anxiogenic drugs on defensive behaviour of mice exposed to an elevated plus-maze.** Nunes-de-Souza, R.L.1,2,5; Sorregotti, T.1,2; Mendes-Gomes, J.1; Rico, J.L.1,3; Rodgers, R.J.4. 1Lab. Pharmacology, School of Pharmaceutical Sciences, São Paulo State University, UNESP, Araraquara, Brazil; 2Joint Graduate Program in Physiological Sciences UFSCar/UNESP, São Carlos, Brazil; 3Lab. Animal Behavior,

Fundación Universitaria Konrad Lorenz, Bogotá, Colombia; 4Behavioural Neuroscience Laboratory, Institute of Psychological Sciences, University of Leeds, Leeds, England. 5Institute for Neuroscience & Behavior-IneC, USP, Ribeirão Preto, Brazil. Exposure of rodents to an open elevated plus-maze (oEPM) elicits antinociception and increases plasma corticosterone levels. However, no studies have yet assessed the defensive behaviour repertoire of animals in this modified test. In Experiment 1, factor analysis was employed to characterise the behavioural profile of mice exposed to the oEPM. Experiments 2 and 3 assessed the effects of acute alprazolam (0.5-1.5 mg/kg; diazepam 0.5-1.5 mg/kg), pentylenetetrazole (10.0-30.0 mg/kg), yohimbine (2.0-6.0 mg/kg), mCPP (0.3-3.0 mg/kg), and acute and chronic fluoxetine (10.0-30.0 mg/kg) and imipramine (1.0-15.0 mg/kg) on behaviours identified in Experiment 1. The factor analyses revealed that behaviour in the oEPM can largely (77% total variance) be accounted for in terms of 3 factors: factor 1 ('depth exploration'; e.g. head-dipping on the arms), factor 2 ('cautious exploration of arms'; e.g. flatback approach), and factor 3 ('risk assessment'; stretched attend postures - SAP). Experiments 2 and 3 showed that, over the dose range used, alprazolam selectively attenuated all measures of defensiveness. Similar, though more modest, effects were seen with diazepam. Confirming the intensity of the emotional response to the oEPM (nociceptive, endocrine & behavioural), relatively few significant behavioural changes were seen in response to the anxiogenic compounds tested. Although acute fluoxetine or imipramine treatment failed to modify behaviour in the oEPM, chronic fluoxetine (but not chronic imipramine) attenuated total flat back approach and increased head dipping outside the central square. Together, the results indicate that the oEPM induces behavioural defensive responses that are sensitive to alprazolam and chronic fluoxetine.

98. **Serotonin-induced postprandial behavior sequence in pigeons (Columba livia): Participation of 5-HT1A receptor**. Dos Santos, TS [1]; Melleu, FF [1]; Krueger, J [1]; Azevedo, F [1]; Poli, A [3]; Marino-Neto, J [1,2]. [1] Dept. Physiological Sciences, CCB, Federal University of Santa Catarina, Florianópolis, Brazil; [2] Institute of Biomedical Engineering, EEL-CTC, Federal University of Santa Catarina, Florianópolis, Brazil. [3] Dept. Pharmacological Sciences, CCB, Federal University of Santa Catarina, Florianópolis, Brazil. Introduction: pharmacological evidences suggest that the serotonin (5-HT) contributes to organize the sequence of postprandial behavior in mammals. Intracerebroventricular (ICV) 5-HT injection in pigeons evokes drinking, hypophagy and sleep-like behavior (SLB). We correlated the 5-HT-mediated responses to activation of 5-HT1A autoreceptors, since ICV injection of 8-OH-DPAT (DPAT) also elicit intense drinking and SLB. Methods: we examined the effects of ICV injections of 5-HT (50 and 150 nmol) and of DPAT (30 nmol) on drinking and SLB in pigeons pretreated ICV with WAY100635 (5-HT1AR antag; 0.1, 0.3 or 1 nmol) or MM77 (post-synaptic 5-HT1AR antag; 23 and 69 nmol). Moreover, the effects of 5-HT and DPAT were also evaluated in pigeons lesioned with ICV bilateral injections (200µg/side) of the 5-HT neurotoxin 5,7-dihydroxytryptamine (5,7-DHT). Results: WAY blocked the dipsogenic effect of DPAT and of the 5-HT 50 nmol dose (without affect the dipsogenic response of 150 nmol). WAY per se evoked increase in the SLB (all doses) and the 1 nmol dose potentiated the hypnogenic response caused by 5-HT. The pretreatment with MM77 dose-dependently decreased the dipsogenic response of 5-HT, but failed in affect the dipsogenic response of DPAT. Moreover, MM77 inhibited the hypnogenic responses of DPAT but left unchanging the effects of 5-HT on SLB. The lesion with the 5,7-DHT abolished the SLB evocked by DPAT, however, neither prevented the dipsogenic effects of 5-HT or DPAT, nor affected the SLB produced by 5-HT. Conclusion: these results suggest the existence of a tonic, 5-HT1AR-mediated inhibitory influence of 5-HT circuits on thirst and sleep in pigeons. However, in serotonergic circuits lesioned animals, neurochemical adaptative changes may occur, which explain the effects of 5-HT1AR activation on drinking and sleep behaviors. Support: CAPES, CNPq, FAPESC.

99. **Microbiota is Essential for Social Development in the Mouse**. Lieve Desbonnet1, Gerard Clarke1,2, Fergus Shanahan1,3 Timothy G. Dinan1,2, John F. Cryan1,4 1Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland 2Department of Psychiatry, University College Cork, Cork, Ireland 3Department of Medicine, University College Cork, Cork, Ireland 4Department of Anatomy, University College Cork, Cork, Ireland. A growing body of data indicate that gut microbiota can influence brain function and development. Germ free (GF) mice have been critical in assessing the role of microbiota in all aspects of physiology. Indeed, GF mice exhibit increases in neuroendocrine responses to stress, decreased neurotrophin levels in the hippocampus and amygdala, reduced anxiety and non-spatial memory, and altered monoamine neurotransmitter levels in the brain. Interestingly, many of the deficits are specific to males. To date, the potential effects of microbiota on social behaviour have not been well investigated despite the fact that neurodevelopmental disorders such as autism have been linked to alterations in gut microbiota. In the 3-chambered sociability test GF mice exhibited significant social impairments, particularly males, as indicated by a lack of the normal preference for time spent in a chamber containing a mouse versus the alternative empty chamber. This was accompanied by reduced preference for novel social situations, where GF mice did not demonstrate the normal increase in time spent investigating a novel over a familiar mouse. Intriguingly, whereas post-weaning bacterial colonisation of the GF mice reversed the observed social avoidance, it had no effect on social cognition impairments. This study shows for, what is to our knowledge, the first time that microbiota are crucial for the programming and presentation of distinct normal social behaviours including social motivation and preference for social novelty. Given that these facets of behaviour are impaired in neurodevelopmental disorders such as schizophrenia and autism and with a similar male preponderance, these data

may have implications for our understanding of the genesis of neurodevelopmental disorders of altered sociability and may lead to the emergence of novel and more effective therapies to combat symptoms in the social domain. The authors and their work were supported by SFI funding.

100. **Decreased dopaminergic neurotransmission produces inverse incentive learning in rats: A role for D1-like receptors**. Richard J Beninger, Kathleen Xu and Tomek J Banasikowski, Queen's University, Kingston ON K7L 3N6 Canada. Increases in dopamine (DA) neurotransmission produce incentive learning, an increased ability of stimuli to elicit responding, but little is known about the effects of decreased DA on learning. We have found that decreased DA neurotransmission produces inverse incentive learning, decreasing the ability of stimuli to elicit responding. A low dose of the DA receptor antagonist haloperidol (0.25 mg/kg ip) failed to produce catalepsy when injected 1 hr before placing a rat in a testing arena with its forepaws resting on a horizontal bar mounted 10 cm above the floor (paired gp). Daily testing with the same dose of haloperidol resulted in catalepsy sensitization so that by day 10, over 60 s of catalepsy was seen. Control rats that receive catalepsy testing each day following saline injection, and haloperidol later in the home cage failed to develop catalepsy (unpaired gp). When both groups were tested with saline, conditioned catalepsy was seen in the paired but not the unpaired gp. When both groups were tested with haloperidol (0.25 mg/kg), catalepsy was seen in the paired but not the unpaired gp. Six days of pre-exposure to the test box preceding the initiation of daily catalepsy testing led to faster development of catalepsy sensitization. This effect was blocked when rats were injected with the DA D1-like receptor antagonist SCH 23390 (0.05 mg/kg ip) 30 min following each pre-exposure session. Results implicate decreased DA in inverse incentive learning and suggest that this form of learning, like incentive learning, depends in part on DA D1-like receptors. (Funded by NSERC)

101. **Quantification by LC-MS/MS of psychotropic drugs in different mice tissues**. Bruno Manadas1,2, Joana Pinto1, Vera M. Mendes1, Ana I.S. Ferreira1,3, Sandra Rocha4, Jorge Costa Pereira3, Graça Baltazar4, David Cotter5, Mike Dunn3. Central nervous system disorders are the third greatest health problem in developed countries, and schizophrenia represents some of the most disabling ailments in young individuals. Schizophrenia (SCZ) is a debilitating and costly disease. While the understanding of the genetic bases of the illness has improved, there is still an only rudimentary knowledge of its pathophysiology. The hippocampus has been strongly implicated in this neuronal disorder, and hippocampal abnormality in SCZ along with dysfunction of the dorsolateral prefrontal cortex plays a relatively central role in the neuropathology of the disorder. Beside the importance of addressing specifically the disease and the brain areas commonly associated with the disorder, it is also of great value to investigate the effect of prescribed drugs. Young male C57BL/6J mice were administered haloperidol, clozapine, citalopram or vehicle, daily via intraperitoneal injections for 1, 2, 4, 8, 15 or 30 days. The cerebrospinal fluid, vitreous humor and blood were collected in EDTA-coated tubes. Brains were quickly removed and dissected. Tissue was dissected bilaterally (prefrontal cortex and hippocampus), and rapidly frozen in TEAB 500 mM with phosphatases and proteases inhibitors on liquid nitrogen and stored at −80 °C until used. Liquid phase extraction protocol was followed by RP-LC-MSMS analysis (Ultimate 3000, Dionex, and 4000 QTRAP, ABSciex) to allow the quantification of the drugs from the different tissues. The analysis of mice body weight shows that although the drugs have different mechanisms of action, all affect the body weight. A liquid-liquid phase extraction method was developed to allow the proper extraction of all drugs using the same protocol followed by reversed-phase liquid chromatography coupled to tandem mass spectrometry. The fragmentation spectra obtained using different collision energies allows the identification of specific fragments used to develop MRM transitions. The developed workflow allows monitoring drug distribution and its metabolization over a wide range of tissues. SCZ patients have a high rate of suicide, and the developed workflow can also be used to search for anti-psychotic treatment from post-mortem collected samples (including vitreous humour and hair).

102. **Ventral midbrain neurotensin sensitizes to amphetamine-induced locomotor activity through activation of extracellular signal-regulated kinases.** 1Rompré, P.-P.; 2Voyer, D.; Lévesque, D2. 1Dept. of Psychiatry, Faculty of Medicine and 2Faculty of Pharmacy, Université de Montréal, Montreal, Québec, Canada, H3C 3J7. Several studies have shown that repeated exposure to amphetamine leads to an enduring enhancement of its behavioral effects, a phenomenon that is dependent upon activation of extracellular signal-regulated kinases (ERK). Since previous studies have shown that repeated ventral midbrain (VM) neurotensin (NT) injections sensitization to amphetamine, we tested the hypothesis that activation of ERK is required for the sensitization effect of NT. Experiments were performed on adult male Long-Evans rats implanted with bilateral cannulae above the VM. On a first experiment different groups of rats were injected on three occasions (day 1, 3 and 5) with vehicle (0.5 ul/side) or D-Tyr[11]NT (1.5 nmol/0.5ul/side) and sacrificed 15 min after the injection on day 1 or day 5. Brains were removed and sliced, and the number of VM neurons expressing phosphorylated ERK (pERK) was measured with immunohistochemistry technique. On a second experiment, different groups of rats were injected on three occasions with vehicle (0.5 ul/side), D-Tyr[11]NT (1.5 nmol/side), U0126 (117 pmol/side), U0124 (117 pmol/side), U0126+NT or U0124+NT and locomotor activity was measured for two hours. Five days later, the locomotor response to a single amphetamine injection (0.75 mg/kg) was measured in all rats. Results show that the number of VM pERK positive neurons was significant larger in NT than in vehicle pre-treated animals on day 1 and on day 5, confirming that NT activated ERK. The locomotor response to amphetamine was

significantly larger in NT pre-exposed animals than in controls, a sensitization effect that was prevented by the MEK antagonist, U0126, but not its inactive analog, U0124. These results replicate previous findings showing that repeated VM NT injections sensitize to systemic amphetamine and demonstrate that this effect is dependent upon activation of the ERK pathway in VM neurons. Supported by Canadian Institutes for Health Research (CIHR, Canada).

103. **Not presented.**

104. **Angiotensin (5-8) induces anxiogenic-like effects in the ventrolateral periaqueductal gray through angiotensin type 1 receptor activation**. Borelli, K.G.1,2,3; Juliano, M.A.5; Prado, W.A.2; Brandão, M.L.3,4; Martins, A.R.1,2 1Instituto de Ciências Biológicas, Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brasil; 2Departamento de Farmacologia, Universidade de São Paulo, Ribeirão Preto, SP, Brasil; 3Instituto de Neurociências e Comportamento, INeC, Ribeirão Preto, SP, Brasil; 4Departamento de Psicologia, Universidade de São Paulo, Ribeirão Preto, SP, Brasil; 5Departamento de Biofísica, Universidade Federal de São Paulo - Escola Paulista de Medicina, São Paulo, Brasil. It has been recognized that the stress-related peptides are involved in anxiety states. The components of the renin-angiotensin system are localized not only in areas related to the regulation of autonomic and endocrine control, but also in brain regions related to the sensory perception, memory processes and stress responses. Among these areas, the ventrolateral periaqueductal gray (vlPAG) is an important structure of the neuronal circuitry controlling the autonomic and behavioral components of emotional states. Angiotensin (Ang) II metabolism in the vlPAG forms several Ang-peptides including Ang (5-8), however, the role of this fragment in the organization of defensive responses and its action mechanisms has not yet been described. For better understanding the related mechanisms, we evaluated effects of intra-vlPAG injections of Ang (5-8) on the exploratory behaviors of the rats in the elevated plus maze (EPM) and the expression of conditioned fear, assessed by the fear-potentiated startle (FPS) and contextual conditioned freezing tests. Intra-vlPAG injections of Ang (5-8) produced, in a dose-dependent manner, a reduction in the entries into and time spent in the open arms of the EPM, decreased direct exploration and increased risk assessment behaviors. Injections of this peptide into the vlPAG before the test session also enhanced contextual freezing and promoted pro-aversive effects in the FPS. We then examined the behavioral effects of intra-vlPAG injections of Losartan, a selective Ang type 1(AT1) receptor antagonist, given prior to Ang (5-8) in the EPM testing. Losartan abolished the behavioural effects produced by the Ang (5-8). These results point to an important anxiogenic-like action for Ang (5-8) in the mediation of defensive behaviors organized in the vlPAG through a process that involves activation of AT1 receptors.

105. **Chronic interferon alpha administration induces thermal hyperalgesia in mice**. Fitzgibbon M.1,3, Burke N.N.1,3, Finn D.P.2,3, Roche M.1,3 1Physiology, 2Pharmacology and Therapeutics, School of Medicine, 2NCBES Galway Neuroscience Cluster and Centre for Pain Research, National University of Ireland, Galway, Ireland. Interferon-α (IFNα) is a cytokine used in the treatment of various cancers and infectious diseases including malignant melanoma and hepatitis B and C, however it has been noted that between 50-70% of treated patients experience depression [4] and/or persistent pain [2]. Enhanced depression- and anxiety-like behavioural responding have been reported in several preclinical models following IFNα administration [1,3], however its effects on nociceptive responding have not been examined. The present study investigated the effect of chronic IFNα administration on depression- and anxiety-like behaviour and nociceptive responding in mice. Male C57Bl6J mice were administered hIFNα (Roferon-A: 400 or 800 IU/g s.c.) or saline vehicle once per day for 22-23 days. Body weight and locomotor activity were assessed over the course of IFNα or saline administration, depressive-like behaviour was assessed in the tail suspension and forced swim tests, and anxiety-like behaviour assessed in the elevated plus maze. Nociceptive responding to a thermal stimulus was assessed using the hot plate test, and the

formalin test was used to evaluate nocicpetive responding to a noxious inflammatory stimulus. Data were analysed by one-way ANOVA followed by Dunnetts post-hoc test and $P<0.05$ was deemed significant. Repeated IFNα administration did not alter body weight or locomotor activity, nor did it significantly induce depressive-like or anxiety-related behaviour. Latency to respond in the hot plate test was reduced in a dose-dependant manner in mice chronic treated with IFNα (400 and 800IU/g), indicating thermal hyperalgesia. In comparison, formalin-induced inflammatory pain behaviour was not altered by chronic IFN-α treatment. The present data demonstrate that repeated IFNα administration did not modulate emotional responding under these conditions but enhanced nociceptive responding to thermal stimuli. These findings indicate that chronic IFNα treatment may alter nociceptive processing leading to enhanced pain perception prior to, or in the absence of, alterations in emotional behaviour. Acknowledgements: Funding received from Molecular Medicine Ireland Clinical & Translational Research Scholars Programme References [1] Fahey B, Hickey B, Kelleher D, O'Dwyer AM, O'Mara SM. The widely-used anti-viral drug interferon-alpha induces depressive- and anxiogenic-like effects in healthy rats. Behav Brain Res 2007; 182:80-7. [2] Nogueira JB, Sena LC, Quintans Jde S, Almeida JR, Franca AV, Junior LJ. Side effects of the therapy with peginterferon and ribavirin in chronic hepatitis C: a small audit. J Pharm Pract 2012; 25:85-8. [3] Siddegowda NK, Kumar Rao NS, Andrade C. Development of a murine animal model of depression for repeated dosing with human interferon alpha. Indian J Psychiatry 2011; 53:239-43. [4] Smith KJ, Norris S, O'Farrelly C, O'Mara SM. Risk factors for the development of depression in patients with hepatitis C taking interferon-alpha. Neuropsychiatr Dis Treat 2011; 7:275-92.

106. **Not presented.**

107. **Not presented.**

108. **Cross-tolerance between nicotine and ethanol is accompanied by increased ethanol self-administration**. John McDaid[1], Ryan A.E. Metz[1], Rinya Kamber[1], Shannon L. Wolfman[2], and Daniel S. McGehee [1,2]. [1]Department of Anesthesia and Critical Care, University of Chicago, Chicago IL, [2]Committee on Neurobiology,

University of Chicago, Chicago, IL. Nicotine and ethanol (EtOH) are two of the most widely abused and co-abused drugs. A major risk factor for alcoholism is tolerance to intoxication which may result in greater EtOH consumption and greater likelihood of addiction. In a number of studies, increased EtOH self-administration is correlated with a decrease in sensitivity to EtOH induced motor impairment. Nicotine EtOH cross-tolerance has been demonstrated in a number of studies, but this has not been correlated with changes in EtOH self-administration. In this study we demonstrate that intermittent nicotine pretreatment in Sprague-Dawley rats results in tolerance to nicotine induced motor impairment and cross tolerance to EtOH induced motor impairment, as assessed using the accelerating rotarod. This cross tolerance to EtOH is accompanied by increased self-administration of a 20% EtOH solution using a 2-bottle choice test. α7 nAChRs are inhibited by EtOH and we have previously demonstrated a role for α7 nAChRs in EtOH induced motor impairment. Further studies will test for possible changes in α7 nAChR sensitivity to EtOH in nicotine EtOH cross-tolerant rats using electrophysiology recording techniques. We will also test a number of nAChR antagonists to assess the role of the nAChRs in general and the α7 nAChR in particular, in the development of nicotine EtOH cross-tolerance and increased EtOH self-administration.

109. **Functional consequences of methylphenidate exposure during postnatal days 11-20 on oxycodone reward in male and female adolescent rats**. Zavala, A.R., Esqueda, M.A., Ojala, K.S., & Langa, R.M. Department of Psychology, California State University, Long Beach. Methylphenidate (MPH) is vastly prescribed in children, and few studies have examined the functional consequences of such early exposure. In rats, early exposure to MPH increases morphine and cocaine effects when rats are tested as adults. However, the consequence of early exposure to MPH on drug reward in adolescent rats has not been investigated. Thus, we examined the effects of early MPH exposure on oxycodone-induced conditioned place preference (CPP), an accepted model of drug reward¬, to determine if early exposure to MPH alters the rewarding effects of oxycodone –a highly abused drug in adolescents. Male and female rats were pretreated with MPH (0, 2 or 4 mg/kg) from postnatal days (PDs) 11-20. Rats were then assessed for oxycodone-induced CPP, beginning on PD 27 (early adolescence) or PD 41 (late adolescence), using an 8-day CPP procedure. During days 1 and 8 of the CPP procedure, rats were tested for their preconditioning and postconditioning place preference, respectively, in 15-minute sessions. During days 3-6, rats were conditioned 30-minutes a day with either oxycodone (0.5 mg/kg) or saline on alternating days. Days 2 and 7 were rest days. Results show that male and female rats tested during early adolescence were unaffected by prior MPH exposure. In contrast, both male and female rats tested during late adolescence exhibited an increasing magnitude of oxycodone-induced CPP. The present data adds to a growing body of evidence that methylphenidate prior to adolescence alters the functional effects of various drugs of abuse later in development.

110. **CB1 receptors in the RVM mediate the antinociceptive effects of the FAAH inhibitor URB597 in Wistar-Kyoto rats**. Kieran Rea 1, Weredeselam Olango 1, Bright Okine 1, Kathleen Coyle 1, Brendan Harhen 2, Michelle Roche 3, David Finn 1 1 Department of Pharmacology and Therapeutics, 2 Department of Chemistry, 3 Department of Physiology, National University of Ireland, Galway. The stress-hyperresponsive Wistar-Kyoto (WKY) rat exhibits a hyperalgesic phenotype in the formalin test compared with Sprague-Dawley (SD) controls. Our recent research has demonstrated that systemic administration of URB597, an inhibitor of the endocannabinoid-catabolising enzyme fatty acid amide hydrolase, suppresses this hyperalgesic response. The rostral ventromedial medulla (RVM) is a critical anatomical component of the descending inhibitory pain pathway and evidence suggests an altered endocannabinoid system in the RVM of WKY rats. Our hypothesis was that enhanced pain-related behavioural responding to intra-plantar formalin injection in WKY rats is mediated by impaired mobilisation of endocannabinoid-CB1 receptor signalling in the RVM. The involvement of the endocannabinoid system in formalin-evoked nociceptive behaviour was investigated in male SD (275-350g) and WKY (275-350g) rats using 0.5mg/kg i.p. URB597, an inhibitor of the endocannabinoid-catabolising enzyme, fatty acid amide hydrolase (FAAH), or the CB1 receptor antagonist/inverse agonist AM251 (3.0mg/kg, i.p.). In a further study, cannulae were stereotaxically implanted 1mm above the RVM of male WKY rats and 5-7 days later, rats received 0.5mg/kg URB597 (i.p.) or vehicle, 45 minutes prior to microinjection of DMSO or AM251 (0.03mM) directly into the RVM. At the end of each study, rats were killed by decapitation, brains were harvested and snap-frozen on dry ice for subsequent measurement of RVM endocannabinoid levels by mass spectrometry, mRNA analysis by RT-qPCR or subsequent verification of cannula placement. The enhanced formalin-evoked nociceptive behaviour of WKY rats was associated with decreased endocannabinoid levels, and increased expression of mRNA for the marker of neuronal activity, zif268 in the RVM. The hyperalgesic response of WKY rats was attenuated by systemic URB597 administration, and this effect was blocked by microinjection of AM251 into the RVM. These behavioural, neurochemical and molecular data indicate that impaired endocannabinoid signalling in the RVM underpins hyper-responsivity to noxious stimuli in a genetic background prone to heightened stress/affect. Acknowledgements: This work was funded by grants from Science Foundation Ireland (10/IN.1/B2976) and The Irish Research Council for Science, Engineering and Technology.

111. **Behavioral characterization of the hallucinogen 2,5-dimethoxy-4-iodophenethylamine (2C-I) and superpotent N-benzyl derivatives**. Halberstadt, A.L.; Geyer, M.A. University of California San Diego, La Jolla, CA, USA. Serotonergic hallucinogens induce their characteristic effects by activating the 5-HT2A receptor. The head twitch response (HTR) is induced by 5-HT2A activation in rodents, and is widely used as a behavioral proxy

for hallucinogen effects in humans. Phenylisopropylamine and indoleamine hallucinogens reliably induce the HTR, but it is not clear whether phenethylamine hallucinogens also consistently provoke this behavior. It has been reported that N-benzyl substitution markedly enhances the 5-HT2A affinity of the phenethylamine hallucinogen 2,5-dimethoxy-4-iodophenethylamine (2C-I). N-benzyl substituted 2C-I derivatives such as 25I-NBOMe (N-(2-methoxybenzyl)-2,5-dimethoxy-4-iodophenethylamine) have recently appeared as designer drugs, but have not been characterized behaviorally. Here, we investigated whether 2C-I and 25I-NBOMe induce the HTR in C57BL6J mice, and tested whether their effects are mediated by 5-HT2A. HTR was assessed using a head-mounted magnet and a magnetometer coil. We also investigated whether 25I-NBOMe alters locomotor activity in C57BL6J mice. 2C-I (1-10 mg/kg SC) and 25I-NBOMe (0.1-1 mg/kg SC) induced the HTR. 25I-NBOMe was 14-fold more potent than 2C-I, and the selective 5-HT2A antagonist M100907 blocked the HTR induced by both compounds. Similar to other 5-HT2A agonists, 25I-NBOMe increased locomotor activity in a dose-dependent manner. These findings confirm that phenethylamine hallucinogens induce the HTR by activating 5-HT2A receptors. Our results demonstrate that 25I-NBOMe is a highly potent derivative of 2C-I, confirming previous in vitro findings that N-benzyl substitution increases 5-HT2A affinity. Given the high potency and ease of synthesis of N-benzyl substituted phenethylamines, it is likely that the recreational use of these hallucinogens will become more widespread in the future.

112. **Nocifensive behavior and neuroendocrine response after nociceptive stimulation in TRPV1 and TRPV4 knockout mice**. Yoichi Ueta, Toru Ishikura, Takanori Matsuura, Mitsuhiro Yoshimura, Jun-ichi Ohkubo, Takashi Maruyama and *Hideo Ohnishi. Department of Physiology and *Orthopedics, School of Medicine, University of Occupational and Environmental Health, Japan. Transient receptor potential protein vanilloid (TRPV) 1 and TRPV4 mainly exist in a sensory nerve, and they are well known as ion channels that are activated by nociceptive stimulation. We investigated nocifensive behavior and neuroendocrine response after subcutaneous (s.c.) injection of formalin (0.5%) using TRPV1 and TRPV4 knockout mice. Nocifensive behavior during phase I (0-10 min after injection) remarkably reduced in TRPV1 and TRPV4 knockout mice, and nocifensive behavior during phase II (10-60 min after injection) significantly reduced in only TRPV1 knockout mice. The number of Fos-like immunoreactivity (Fos-LI) neurons in the laminae I-II of the dorsal horn (L4) and in the paraventricular nucleus of the hypothalamus in TRPV1 knockout mice reduced but not significantly different from that of TRPV4 knockout mice and wild type mice after s.c. injection of formalin. Next, we investigated nocifensive behavior and neuroendocrine response after s.c. injection of TRPV4 agonist, 4α-phorbol 12,13-didecanoate (4α-PDD) (500μM). Nocifensive behavior after s.c. injection of 4α-PDD didn't increase significantly compared to nocifensive behavior induced by s.c. injection of saline in TRPV1 knockout mice, TRPV4 knockout mice and wild type mice. The number of Fos-LI in the dorsal horn increased significantly in TRPV1 knockout mice and wild type mice after s.c. injection of 4α-PDD. These results suggested that the activation of both TRPV1- and TRPV4-expressing neurons caused by s.c. injection of formalin induced remarkable nocifensive behavior but the independent activation of TRPV4-expressing neurons caused by s.c. injection of 4α-PDD didn't induce nocifensive behavior just induced Fos in the dorsal horn of the spinal cord.

Friday, June 28

8:30-10:30 **Symposium: Sex matters: Developmental influences have sex-dependent long-term consequences for behavior.** Chair**: Susanne Brummelte.** *Guttenberg Suite*

8:30 **Contributions of hormones and genes to the sexual differentiation of song and partner preferences.** Michelle Tomaszycki/Wayne State University. Perhaps the most important decision in a monogamous animal's life is the choice of a partner. In birds, partner preferences are sexually differentiated and learned over long periods of time. Partner preferences involve visual and vocal signals, and adult zebra finches are able to make sophisticated judgments based on both types of signals. However, the neural mechanisms underlying the development of this complex process are not well understood. We do know that circulating sex steroids cannot alone account for these behaviors. Our research focuses on the complex interplay between hormones and genes acting in different neural circuits to produce sex differences in behavior. In the song system (males sing, females do not), we have identified many genes that are male-biased during development. At least one of these genes, a sex steroid metabolizing gene, is up-regulated by estradiol treatments. In contrast, this same gene is female-biased in visual and vocal perception regions on the brain. Our research suggests that genes and hormones play a role in the sexual differentiation of partner preferences, song and song perception and provides clues to the complex role of learning, hormones and genes in the development of learned behaviors.

8:54 **Early programming of stress-related alterations: Sex differences, molecular mechanisms and pharmacological implications for depression and addiction.** Sara Morley-Fletcher, PhD University Lille North of France Neuroplasticity Team - CNRS UMR 8576/ UGSF Structural and Functional Glycobiology Unit. The effects of stress on the brain have long been associated with the onset and exacerbation of several neuropsychiatric disorders such as depression, anxiety and drug addiction. Early life stress causes long-lasting changes in neuroplasticity and behavior that result into an increased vulnerability to such stress-related disorders in the adult life. The model of prenatal restraint stress (PRS) in rats is a clear example of early programming of stress- related disorders. In particular, PRS rats, i.e. the offspring of mothers exposed to repeated episodes of stress during pregnancy, show critical neurobiological and behavioral alterations reminiscent of an anxious/depressive phenotype, such as altered feedback mechanisms of the HPA axis, impaired hippocampal neurogenesis, a selective impairment of the glutamate machinery, high levels of "anxiety" and altered circadian rhythms, as well as enhanced sensitiveness to natural reward or to the effects of psychostimulant drugs. Interestingly, several changes in hippocampal neuroplasticity induced by PRS are critically sex-dependent, and the anxious behavioral outcome may diverge in males and females, with males being more anxious. On the other hand, depressive-like features and response to cocaine seem to be equally affected by PRS in both sexes. PRS exerts a strong impact on rat preference to natural rewards and dihydrotestosterone for PRS males and estradiol for females appear to play a pivotal role in shaping this behavior. Despite the permanent imprinting induced by early stress, the dysfunctions observed after PRS can be reversed by environmental or pharmacological strategies such as environmental enrichment, chronic antidepressant treatment and sex hormones supplementation.

9:18 **Sex-specificity in transgenerational epigenetic programming.** Bale, T. University of Pennsylvania. Neurodevelopmental disorders including autism and schizophrenia show strong sex biases in presentation, onset and treatment. Such disorders have been associated with fetal antecedents including maternal stress. The programming mechanisms through which stress contributes to disease development are not well understood; though likely involve a complex interaction between the maternal environment and effects on the placenta. We have previously identified a sensitive period of early gestation where maternal stress produces sex-dependent epigenetic programming effects on offspring stress pathway neurodevelopment. Our recent studies have focused on examining the upstream signaling mechanisms that associate changes in the maternal hormonal milieu with reprogramming of the fetal brain. To identify potential biomarkers, we conducted analyses by Affymetrix Array in male and female placentas across pregnancy to determine genes that had sex-specific expression and were affected by maternal stress. One candidate gene, O-glycosyltransferase, was identified and further examined for its role in altering neurodevelopment by biochemical, proteomic and genomic analyses. ChIP analyses further identified a reduced association with the transcriptional activational mark, H3K4me3, with this gene, decreasing its expression in stressed male placentas. This X-linked gene was similarly regulated in human placental tissue supporting its translational potential. To link this placental gene with an effect in re-programming the developing hypothalamus, we examined gene expression patterns at PN2 in mice with a placental-specific targeted reduction or deletion in OGT. Females hemizygous for placental OGT showed a dramatic shift in hypothalamic gene expression compared to control females, supporting a critical role for this gene in placental function important in neurodevelopment. These results may provide critical insight into the mechanisms contributing to sex-biased disease vulnerability to maternal stress during early pregnancy impacting the developing brain via effects at the placenta that are transmitted to reprogram critical neuroendocrine systems.

9:42 **Sex matters: Developmental perturbations result in sex-dependent long-term consequences on neuroplasticity, behavior and HPA function**. Liisa Galea and Susanne Brummelte. University of British Columbia, Vancouver, Canada. Early adversity effects on neuroplasticity and behavior extend well beyond the gestational period. Exposure to stress during adolescence and/or high levels of maternal corticosterone perinatally elicit sexually-dimorphic

effects in 'emotionality' and hippocampal neurogenesis in adult male and female rodents. The hippocampus is a highly plastic brain region containing a significant number of steroid receptors and retains to produce new neurons throughout the lifespan. Importantly, the hippocampus is vulnerable to the effects of stress and is implicated in depression. We examined the impact of high maternal glucocorticoid exposure during gestation or the postpartum on the development of male and female offspring and in separate experiments the effects of stress or high glucocorticoids during adolescence. Stress during adolescence reduced hippocampal neurogenesis and increased basal corticosterone levels in adult female, but not male, rats. The adult offspring of dams exposed to high maternal CORT in utero, but not during the postpartum, showed more depressive-like behavior compared to controls. However adult males, but not adult females, of dams exposed to high maternal CORT postpartum exhibited more anxiety-like behavior than controls. Offspring from dams exposed to CORT during gestation had lower basal CORT and higher stress levels of CORT, and these findings were stronger in adult female offspring. Together these studies show that sexes differ in neuroplasticity and behaviour in response to steroid hormone perturbations during early and later development which may provide insight into why the sexes are differentially more vulnerable to stress-related disorders such as depression, substance abuse disorders and anxiety-related disorders. Research supported by CIHR to LAMG.

10:06 **Fetal programming: Sex-specific and transgenerational consequences.** Stephen G. Matthews/University of Toronto. The developing fetus remains very sensitive to its environment throughout gestation. The fetus is highly responsive to both nutritional and endocrine cues. Glucocorticoids are critical for normal development and are tightly regulated at low levels in the fetus through gestation. However, levels increase rapidly near term. This surge is critical for lung development and maturation of other organ systems including the brain. Fetal glucocorticoid concentrations may be elevated as a result of maternal or fetal stress. A very large number of human fetuses are exposed to high levels of synthetic glucocorticoid (sGC). Over 10% of pregnant women are treated with sGC to promote lung development in fetuses at risk of being born preterm. The fetal brain is highly sensitive to the influences of glucocorticoids, which can rapidly transform the transcriptional landscape in critical structures such as the hippocampus. Glucocorticoid exposure has been shown to result in life-long changes in the regulation of hypothalamo-pituitary-adrenal (HPA) function and behaviour in the offspring of several species including humans. The natural glucocorticoid surge as well sGC exposure have profound effects on the fetal hippocampal transcriptome and epigenome (methylation and acetylation), and sGC exposure can produce life-long changes in DNA methylation. Further, prenatal exposure to sGC can have transgenerational effects on growth, HPA function and behaviour.

8:30-10:30 **Symposium: Lost in translation: Improving the predictive validity of animal models for CNS disorders.** Chair**: David McKinzie**. *Tara Suite*

8:30 **Leveraging 60 years of monoamine antipsychotic experience: reducing clinical phase II failures for new schizophrenia medications**. David McKinzie. Eli Lilly & Company. All current medications for the treatment of schizophrenia are mixtures of biogenic amine pharmacology with dopamine D2 receptor antagonism serving as the common element. Although these medications are unequivocally useful in controlling symptoms of schizophrenia, significant unmet clinical need exists for both efficacy and tolerability. Thus, new medications with novel mechanisms of action are needed to advance our treatment of schizophrenia. However, to date, no new medication lacking dopamine D2 activity has successfully demonstrated adequate efficacy in large clinical trials despite robust preclinical data. In this talk, I will highlight key issues that are believed to underlie the failure to translate preclinical antipsychotic-like activity of novel treatments into clinical efficacy and what steps are being taken to improve clinical attrition.

9:00 **Getting Smarter about Developing Drugs to Treat Cognitive Deficits in CNS Disorders: The use of Touchscreens in Drug Discovery.** Sophie Dix. Eli Lilly & Company, Windlesham, UK. The Pharmaceutical industry has not been very successful at bringing drugs to treat cognitive deficits to the clinic. Currently there are only two classes of compounds licensed for the treatment of cognitive symptoms in Alzheimer's disease (AD) and none for cognitive impairment associated with schizophrenia. Compare this with over 70 drugs representing at least 16 classes for affective disorders such as depression and anxiety. The pharmaceutical industry has had an over reliance on poorly defined high throughput assays with poor sensitivity, specificity and translational potential. Touch screen (TS) equipped operant chambers are becoming increasingly popular in both academia and industry. These confer significant advantages over traditional lever-equipped operant chambers due to the range of stimuli that can be presented to the animal. This allows multiple paradigms to be developed that can tap into a variety of cognitive domains allowing assessment of e.g. attention, learning and memory, spatial and non-spatial recognition memory using the same equipment and possibly even in the same animal. Furthermore, there is translational potential to have analogous paradigms across species including humans.TS technology has been widely adopted across industry; rapid validation of new tasks is being made easier through large consortia such as the Innovative Medicines Initiatives: New Meds (schizophrenia) and PharmaCog (AD). Multi-site experiments allow for novel protocols to be further developed, harmonized and validated rapidly with the aim of identifying translatable paradigms that are sensitive, for example, to AD pathology in transgenic mice and hence can be used in drug development and research into MCI and AD.

9:30 **Moving beyond current behavioral antidepressant animal models: Back translation of recent clinical findings to the bench.** Jeffrey M. Witkin Lilly Research Labs. As with most areas of pharmacotherapeutics, a

significant percentage of patients are not fully served by existing medicines in the area of major depressive disorder (MDD). Only about one third of patients respond to current antidepressants and less than one third display symptom remission. Another third of the patients do not respond to multiple therapeutic interventions (treatment resistant depression or TRD) leaving a huge unmet medical need in a disease area that affects millions of people each year. Since the original report by Berman and colleagues and its subsequent replication by Zarate et al. in 2006, at least 35 reports now exist on the efficacy of ketamine in alleviating symptoms in TRD patients. Positive findings have also been disclosed on other NMDA receptor antagonists and modulators as well as on scopolamine (Drevets and colleagues) in addition to a host of other drugs (e.g., buprenorphine and other drugs). Efficacy in humans can enable back translation into the preclinical laboratory. What are the key biological actions of ketamine and other TRD therapeutics that enable relief from TRD? The present discussion will focus on the convergent biological actions of TRD therapeutic agents in patients and non-human species that might facilitate the treatment for those patients currently not responding to standards of care.

10:00 **Mining and modeling human genetics in the search for autism therapeutics.** Daniel Smith/Autism Speaks, Inc. Autism spectrum disorders (ASD) are a family neurodevelopmental disorders with prevalence estimated to be approximately 1% worldwide. The core symptoms are social and communication impairments and repetitive, restricted behaviors and interests. Psychiatric, neurological and somatic symptoms and comorbidities are common in individuals with ASD. The current standard of care is intensive behavioral intervention. Off-label use of psychotropic drugs for the treatment of associated symptoms is widespread in the autism community, but there is little scientific evidence supporting their use. Moreover, no medications are approved for the treatment of the core symptoms of autism. There are many potential etiologies of ASD, and knowledge of the genetic origins from large-scale studies in humans is rapidly evolving. Research on the impact of ASD risk mutations on synaptic function have begun to reveal molecular pathways and potential therapeutic drug targets. The use of animal models to characterize ASD risk genes has proved to be valuable for defining affected cellular mechanisms and brain circuits. Researchers using neurophysiological and functional brain imaging techniques have revealed notable differences between individuals with ASD and unaffected control subjects. These studies point to specific brain circuits and patterns of activity that can be evaluated with complimentary techniques in preclinical and clinical domains. Studies that combine models of human genetics and translational neurophysiological outcome measures will be an important test of the back-translational approach to developing novel therapeutics for ASD.

10:30-11:00 **Coffee/Tea Break**. *Tara Suite*

11:00-12:00 **Presidential Lecture: D. Caroline Blanchard, Ph.D., University of Hawaii, Honolulu, HI, USA. The joy of a good model: Autism, heparan sulfate, and the BTBR mouse.** *Tara Suite*

The joy of a good model: Autism, heparan sulfate, and the BTBR mouse. D. Caroline Blanchard University of Hawaii. Autism spectrum disorders (ASD) are defined in terms of aberrant social and communicatory behaviors as well as enhanced stereotypy and ritualization of specific behaviors or interests. Our lab's attempts to produce a description of how these differences might be expressed in mice, in order to evaluate their value as animal models of autism, have resulted in detailed behavior analyses applied to a variety of mouse strains. Results suggest that the BTBR T+tf/J (BTBR) mouse shows the most robust and comprehensive autism-relevant behavior phenotype of all those we have tested, suggesting that its biology may also reveal insights into the biology of idiopathic autism. BTBR mice show a widespread disturbance in the molecular composition of the extracellular matrix in the subventricular zone of the lateral ventricles (LV-SVZ), compared to C57BL/6J (control) mice. Deep reductions in heparan sulfates (HS), linear polysaccharides that interact with a range of growth and guidance factors in the LV-SVZ, and in laminin, suggest a potential mechanism and brain location involved in the disturbed hodology of the autistic brain. Evaluation of this hypothesis involved 4 pairs of autism-diagnosed individuals (ADI) with age- and sex- (all male) matched typically developing (TD) controls. In the TD controls, HS levels declined sharply with increasing age, consonant with a particular function for HS in the developing brain. Overall, ADI had significantly less HS than TD, but this difference was most profound in the younger samples, disappearing in the age 60+ pair. Laminin levels were consistent for TD, but extremely variable for ADI. We now have a total of 18 ADI-TD age- and sex-matched pairs, and are examining gene expression and DNA methylation profiles in the LV-SVZ of individuals diagnosed with autism. We expect that changes localized to the LV-SVZ will provide greater specificity concerning epigenetic factors involved in the brain dysfunctions associated with autism.

12:00-1:30 **Break**. **Meet The Professionals Lunches.**

1:30-3:30 **Symposium: Molecular and cellular endophenotypes in neuropsychiatric disease: Homer proteins.** Chairs: **Karen K. Szumlinski; Tod E. Kippin.** *Guttenberg Suite*

1:30 **Dopamine-glutamate interaction, antipsychotics and Homer.** Andrea de Bartolomeis, Laboratory of Molecular and Traslational Psychiatry University School of Medicine of Naples Federico II. Introduction. Dysfunction of dopamine- glutamate interaction has been suggested to be relevant both in psychosis pathophysiology and

pharmacological treatment. Among multiple effectors at postsynaptic density (PSD) Homers play a crucial role in the complex architecture of excitatory synapses and in dopamine-glutamate interaction. Here we report a series of preclinical experiments aimed to image quantitatively the topography and transcripts expression of Homer splicing variants in functionally related brain regions after acute and chronic treatment with antipsychotics or other compounds that may perturbate dopamine-glutamate interaction. Methods. Molecular imaging of Homer and other PSD protein transcripts, was performed on rat brain sections after ,in vivo, treatment with antipsychotics (APS) (haloperidol, risperidone, olanzapine, quetiapine, aripiprazole, sulpiride, amisulpride), a dopamine indirect agonist (GBR 12909) and a NMDA receptor antagonists (Ketamine, MK 801, memantine) both in acute and chronic paradigms. For distribution analysis autoradiographic signal intensity of Homer1a expression by each APS has been analyzed as a function of striatal regions. The spatial distribution profiles were analyzed by a correlation-based clustering with a novel quantitation method. Results. The relative amount of Homer1a could be differentiated in discrete sub-groups according to the pattern of transcripts' expression in striatum induced by antipsychotics. Maximum induction was triggered by haloperidol and 10mg/kg ziprasidone. The second group comprised ziprasidone 4 mg/kg and aripiprazole 12 mg/kg, which elicited moderate-to-high levels of Homer1a expression. The third group included aripiprazole 30 mg/kg, quetiapine 30 mg/kg, risperidone, sulpiride, and olanzapine, which induced moderate levels of Homer1a expression significantly higher than vehicle in some striatal sub-regions only. Quetiapine 10 mg/kg, clozapine, and sertindole elicited poor expression. Finally different doses of amisulpride (10 vs. 35 mg per kg) exert distinct effects possibly as a consequence of the suggested preferential pre- vs. postsynaptic blockade of D2-like receptors. Conclusions: Comparative analysis showed that among PSD proteins higher levels of Homer1a induction may be related to the dose of APDs as well as D2 receptor affinity and 5HT2a receptor blockade. Topographic distribution analysis demonstrated that Homer1a expression is consistent with a striatal gradient resembling the distribution of medium-sized-spiny neurons and, possibly, of D2 receptors.

2:00 **Homer as a regulator of pain sensitivity and heroin-induced rewarding effect.** I. Obara 1,2, and K.K. Szumlinski1. 1Department of Psychology, University of California, Santa Barbara, USA 2 School of Medicine, Pharmacy and Health, Division of Pharmacy, University of Durham, Queen's Campus, Stockton on Tees, UK. Group1 metabotropic glutamate receptors and Homer proteins regulate glutamate transmission modulating behavioral sensitivity of chronic pain and drugs of abuse. Using a combination of behavioral genetics and immunoblotting approaches we delineated the relative roles played by different Homer isoforms, including their interactions with mGluR5, in the development of neuropathic pain induced by sciatic nerve ligation and consequent effects on heroin-induced place-conditioning (CPP). Briefly, immunoblotting studies on wild-type (WT) mice showed that nerve injury elevated spinal dorsal horn and accumbens Homer1b/c level that was accompanied by increased expression of mGluR5 and NR2a. Behavioral studies revealed that relative to WTs, Homer1a knock-out (KO) and transgenic (Tg) mice with reduced mGluR-Homer binding (mGluR5F1128R, mGluR5T1123A/S1126A) exhibited increased allodynia. Additionally, heroin elicited robust CPP in uninjured WT mice and conditioned place-aversion (CPA) in neuropathic WTs. Interestingly, with the exception of the mGluR5F1128R, all uninjured mutant lines exhibited heroin CPP, but neuropathic mice failed to develop heroin CPA. When Homer protein levels were modulated by intra-accumbens virus-mediated gene transfer of Homer1c cDNA or siRNA, AAV-Homer1c produced, while shRNA-Homer1c prevented against, heroin CPA in neuropathic mice. These indicate that different Homer isoforms appear to play distinct roles in regulating the processing of chronic pain, which may have relevance to our understanding of its etiology and treatment. Moreover, accumbens Homer proteins and Homer-mGluR5 interactions are important for the development of opioid-dependent neuroplasticity of relevance to opioid addiction. Supported by UCSB funds to KKS.

2:30 **Homer2: A molecular trigger for alcoholism?** Karen K. Szumlinski, University of California, Santa Barbara, CA, USA. The Group 1 metabotropic glutamate receptors (mGluR1/5) are increasingly implicated in regulating various aspects of addiction-related behavior, including binge alcohol drinking. However, the downstream mechanisms involved in the "anti-addictive" properties of Group 1 mGluR antagonists are less clear. To this end, our laboratory seeks to understand the role for the Homer family of Group 1 mGluR scaffolding proteins in the development and maintenance of excessive alcohol intake and to investigate potential roles for mGluR/Homer-mediated activation of G alpha q and beta-gamma signaling in binge alcohol drinking. This presentation will summarize behavioral pharmacological, genetic and proteonomic data implicating idiopathic and alcohol-induced increases in the activational state of Group 1 mGluR-Homer2-kinase pathways within several extended amygdala structures in the manifestation of binge alcohol drinking behavior of relevance for our understanding of the pathophysiology of alcoholism.

3:00 **Role of Homer2 in regulation of adult neurogenesis: Implications for corticolimbic striatal function.** Kippin, TE, University of California, Santa Barbara. The discovery that the adult brain is capable of generating new neurons in a regionally specific manner has prompted investigations of potential regulators of adult neurogenesis. Research has indicated that proliferation in the hippocampus and subventricular zone are modulated by the glutamatergic system in a receptor specific fashion. Homer2 is a scaffolding protein involved in the regulation of glutamate signaling in the brain with loss of Homer 2 function producing deficient coordination between ionotropic and metabotropic glutamate receptors. Transgenic Homer 2 knockout (KO) animals also show regionally specific reductions in basal glutamate levels. Interestingly, Homer 2 KO mice also show enhanced contextual conditioning for cocaine, suggesting that Homer2 loss may be alter hippocampus function, an area with high adult neurogenesis. . The aim of the current experiment was to investigate the effects of Homer2 KO on cell proliferation in the hippocampus and subventricular zone. At 10-12 weeks

of age, Homer 2 KO and wildtype mice were injected with bromo-deoxyuridine (BrdU; 60mg/kg, IP once every 3 hours for a total of 5 injections). The mice were sacrificed 4 weeks later, and long term BrdU retention was used to assess the proliferation in the subventricular zone of neural stem cells (NSC) and cell genesis in the dentate gyrus of the hippocampus. Homer 2 KO mice showed significantly more BrdU-labeled cells in both regions indicating that proliferation or survival in the adult brain is increased in the absence of Homer2. Conversely, no differences were observed in the number of primary neurospheres derived from the subventricular zone were seen, suggesting that the size of the NSC population was not altered. Together, these findings indicate that Homer 2 plays a role in glutamatergic regulation of adult neurogenesis and that loss of Homer2 enhances proliferation and/or survival of neuroprecusors.

1:30-3:30 **Symposium: Revisiting the role of medial septal neurons in learning and memory. Chair: Kevin Pang.** *Tara Suite*

1:30 **Role of GABAergic medial septal neurons in working memory.** Kevin Pang, Department of Neuroscience, New Jersey Medical School and Veterans Affairs Medical Center, New Jersey Health Care System. The medial septum and diagonal band of Broca (MSDB) have a profound influence on hippocampal activity and function. The MSDB includes cholinergic, GABAergic, glutamatergic and peptidergic neurons. From a behavioral perspective, most research to date has focused on the cholinergic neurons; these neurons make projections to the hippocampus and other limbic structures. Our research is focused on understanding the role of the GABAergic MSDB neurons in learning and memory. Initially, low doses of kainic acid were infused into the MSDB to preferentially damage GABAergic but not cholinergic MSDB neurons. More recently, the selective immunotoxin GAT1-saporin is being used, but our results are similar between toxins. GABAergic MSDB damage does not impair rats learning traditional water maze procedure. In contrast, rats are impaired in spatial working memory. Our results suggest that proactive interference is enhanced following damage of GABAergic MSDB neurons, an impairment that may be related to the reduction of hippocampal theta rhythm following lesions. In addition to damaging GABAergic septohippocampal neurons, we also show that cholinergic release in the hippocampus is impaired under conditions where cognitive demand is high but not when it is low. Thus, our current hypothesis is that GABAergic MSDB neurons are important for working memory by reducing proactive interference. The importance of GABAergic MSDB neurons in cholinergic function and the role of the cholinergic system in cognition is being investigated.

2:00 **Septohippocampal GABAergic neurons and consolidation of memories.** Jean-Christophe Cassel, Julie Koenig, Lucas Lecourtier LNCA, UMR 7364 Université de Strasbourg-CNRS, Faculté de Psychologie, 12 rue Goethe, F-67000 Strasbourg (France). Consolidation at system level involves functional exchanges between the hippocampus, which stores recent memories, and the prefrontal cortex, which, over time, becomes the depositary of remote memories. It is difficult, however, to conceive that this process operates independently of other structures. We established that after selective lesions of septal cholinergic (192 IgG-saporin) or GABAergic (orexin-saporin) neurons, or their combination, rats acquired the platform location in a water maze normally and retrieved this information 1 day after training. At a 5-day delay, those with GABAergic lesions performed at chance level, but those with cholinergic lesions still performed well. At the 25-day delay, both types of lesions had resulted in memory loss. These observations suggest a sequential implication of the GABAergic and cholinergic neurons of the medial septum in system consolidation of remote memories. In another study, we established that the activation of 5-HT1A receptors in the medial septum impaired water maze learning. Indirect evidence suggests that the 5-HT1A receptors to be implicated in this alteration could be on GABAergic neurons. Our results are in line with the idea that processes contributing to memory formation, including that of remote memories at the system level, do implicate structures other than the prefrontal cortex and the hippocampus. The medial septum and its GABAergic neurons projecting to the hippocampus could be one of them.

2:30 **Cholinergic and noncholinergic functions of the hippocampus in episodic memory.** Easton, A. Durham University, UK. Recent developments have allowed us to test episodic memory in animals. Using our 'what-where-which occasion' task (object-place-context) we tested rats with specific lesions of the cholinergic input to the hippocampus. These animals were unimpaired at the task, but counterintuitively impaired in a 'where-which' (location-context) version of the same task. The ability to perform normally on the episodic task is despite animals with fornix or hippocampus lesions being impaired. Similarly, 3xTgAD mice are impaired at the task when pathology is limited to the hippocampal region. The task behaves like episodic memory in humans - leading to the conclusion that acetylcholine in the hippocampus is not necessary for episodic memory. However - acetylcholine in the hippocampus is necessary for some associative recognition tasks, and this dissociation may allow us to better understand its function.

3:00 **Alterations in cholinergic and noncholinergic basal forebrain neurons in aging: Consequences for cognition.** Jennifer Bizon, Department of Neuroscience, Evelyn F. and William L. McKnight Brain Institute, University of Florida, Gainesville, FL, USA. Learning, memory, and executive functions supported by hippocampus and prefrontal cortex are vulnerable to decline across the lifespan; however, the critical neural mechanisms that underlie such loss of function are still not well-understood. A large literature suggests a role for basal forebrain neurons that innervate these cortical fields and, specifically, has linked the degeneration of basal forebrain cholinergic neurons to some aspects of cognitive decline. Substantially less is known regarding the status of codistributed GABAergic neurons and their contribution to cognitive deficits in aging. Notably, GABAergic basal forebrain neurons preferentially innervate cortical

interneurons, positioning them as important regulators of cortical inhibition. In a series of studies using electrophysiological, biochemical, and pharmacological approaches, we have identified pronounced alterations in cortical inhibitory circuitry and signaling that contribute to the emergence of age-related deficits in spatial memory, working memory, and attentional set-shifting. Moreover, a recent stereological study conducted in basal forebrain of behaviorally characterized young and aged rats surprisingly revealed that the number of neurons expressing the GABA synthesizing enzyme, GAD67, is robustly and selectively elevated in aged cognitively-impaired rats. These data suggest that alterations in GABAergic afferents from basal forebrain contribute to disruptions in cortical excitatory/inhibitory dynamics and cognitive dysfunction at advanced ages. The basal forebrain GABAergic neurons may represent a unique target for improving some forms of age-related cognitive decline. Funding sources: AG029421 and McKnight Brain Research Foundation

3:30-4:00 **Coffee/Tea Break**. *Tara Suite*

4:00-6:00 **Symposium: Contribution of early environmental and genetic susceptibility to behaviour related to adult psychopathology.** Chairs: **Mikhail Pletnikov; John Waddington**. *Tara Suite*

4:00 **Searching for early determinants of emotional reactivity and neuroendocrine responses to stress in animal models: From mice to non human primates.** Francesca Cirulli Section of Behavioural Neuroscience, Department of Cell Biology and Neuroscience, Istituto Superiore di Sanità, Rome, Italy (francesca.cirulli@iss.it) In humans, both genetic and experiential factors can shape individual vulnerability to psychiatric illness. Among the many factors involved in brain development and function, neurotrophins appear as good candidates for mediating long-term effects of experience on brain function. We have used a comparative approach using both rodents and primates (rhesus macaques) to test the hypothesis that changes in the levels of neurotrophins (i.e., Nerve Growth Factor -NGF and Brain-derived neurotrophic factor - BDNF) during critical periods of brain development, as a result of different rearing experiences, might impair the ability to cope with stress, thus promoting psychopathology. We have shown that, in rodents, early interaction with mother and peers can independently build adult social skills and affect brain BDNF levels. In parallel with these studies, we have characterized a single nucleotide polymorphism (SNP) in rhesus macaques, which results in a Val to Met transition in the pro-BDNF domain, similar to a well described variant in the human gene. We subsequently tested the hypothesis that peripheral levels of BDNF, which is involved in the response to stress and in the pathophysiology of anxiety and depression, might be differentially affected in a non-human primate model of early adverse rearing in a genotype-dependent manner. Males and females rhesus macaques reared either with their mothers (MR), in peer-only groups (PR), or in a "surrogate/peer-reared" (SPR) condition with limited peer interactions, were used as experimental subjects. Results from these studies indicate that a SNP, which results in a Val to Met transition in the pro-BDNF domain, is present in rhesus macaques and is able to affect BDNF peripheral levels in a gene x environment manner. Implications for such context-dependent changes in the expression of key genes affecting brain development and plasticity will be discussed.

4:30 **Brain dysfunction induced by chronic stress in early life: Involvement of the stress-sensitive transcription factor NPAS4.** Kiyofumi Yamada, Nagoya University, Japan. Neuronal PAS domain protein (Npas) is a neuron-specific transcription factor, and its expression level in the hippocampus is regulated by depolarization. Recent studies have demonstrated that Npas4 regulates the development of GABAergic inhibitory synapses and transcription program for contextual memory formation in the hippocampus. We have previously reported that mRNA levels of Npas4 are decreased in the hippocampus of mice following chronic social isolation or restriction stress, both of which induce impairments of hippocampus-dependent memory accompanied by the decrease in adult neurogenesis in the dentate gyrus. We suggested that Npas4 may contribute to the impairments of adult neurogenesis in the hippocampus, memory and emotional behaviors induced by chronic stress. However, the transcriptional regulation by stress of Npas4 gene as well as its role in neuronal function remains to be elucidated. Here we show that transcription of Npas4 gene is down-regulated by stress through the binding of agonist-bound glucocorticoid receptor (GR) to putative negative glucocorticoid response elements (GREs) as well as DNA methylation of the promoter. Furthermore, it is demonstrated that Npas4 increases Cdk5-dependent phosphorylation of synapsin I, which is associated with neurite elongation in Neuro2a cells and primary cultured neurons. Npas4-KO mice show PPI deficits in adulthood. Our findings suggest that Npas4 plays an important role in the structural and functional plasticity of neurons and may be a potential new drug target for stress-related neuropsychiatric disorders.

5:00 **Gene-environment interplay across the lifespan: Investigating etiopathological processes in schizophrenia using mutant models of gene disruption.** Colm O'Tuathaigh, School of Medicine University College Cork. Several genes have been associated with risk for schizophrenia, together with exposure to specific environmental factors at various points in the life span. Intrauterine adversities, biological insults [e.g. infection, trauma and cannabis exposure] and psychosocial stressors [e.g. urbanicity, social defeat] over infancy, childhood and adolescence appear to interact with genetic factors to determine risk for psychotic illness. Translating epidemiologically-relevant environmental factors into current preclinical gene × environment [G - E] models constitutes a particular challenge. Few studies using genetic mutant models have examined the role of G - E interactions in schizophrenia. Neuregulin-1 is a schizophrenia risk gene that is critical for brain development, such that any interaction with environmental adversity may provide further insights

into the origins of the disease. Recent studies in our laboratory have investigated how NRG1 genotype may modify the effects of (a) maternal immune challenge on development of schizophrenia-related phenotypic features in adult offspring, (b) exposure to social defeat during adolescence on same. The catechol-O-methyltransferase (COMT) gene, located on chromosome 22q11.2, encodes the COMT enzyme that plays a key role in regulating dopamine availability in prefrontal cortex. We have also examined how COMT genotype may modify the consequences of adolescent exposure to cannabis. It is proposed that such preclinical studies of putative gene-environment interactions will prove of considerable translational value, providing new targets and hypotheses upon which to base clinical psychiatric research.

5:30 **Interaction of mutant DISC1 with environmental adversities: Shared and unique mechanisms.** Mikhail Pletnikov, John Hopkins University School of Medicine, Baltimore, USA. Background: Multiple adverse environmental factors contribute to the pathogenesis of schizophrenia via complex interactions with genetic risk factors in susceptible individuals. We have been modeling complex etiologically relevant gene-environment interactions in mice that selectively express mutant Disrupted-In-Schizophrenia 1 (DISC1) in neurons or astrocytes and are exposed to toxins, substance of abuse, postnatal stress or immune challenges at different time points across the life span. Methods: Mice that express mutant DISC1 in forebrain neurons were prenatally exposed to immune challenge with poly I:C or low doses of Pb2+ or were chronically treated with delta-9-tetrahydrocannabinol (Δ9-THC) during adolescence. We evaluated the neurobehavioral, neuroimmune and molecular phenotypic changes in adult mice. In addition, mutant mice with selective expression of DISC1 in astrocytes were exposed to early postnatal stress and hippocampal adult neurogenesis and depression-related behaviors were also assessed later in these animals. Results: Prenatal immune activation in DISC1 mice resulted in the brain and behavioral alterations that were consistent with aspects of mood disorders. Developmental exposure to Pb2+ produced schizophrenia-like behavioral alterations that could be ameliorated with D-serine treatment, suggesting the involvement of NMDA synaptic neurotransmission. Chronic adolescent exposure to THC led to mild cognitive impairment in mutant DISC1 mice. Astrocytic expression of mutant DISC1 was accompanied by dysregulation of immune and D-serine pathways and decreased adult hippocampal neurogenesis that was associated with emotional and cognitive abnormalities expected to be exacerbated with postnatal exposure to stressful events. Conclusions: Our studies suggest that both shared and cell type specific alterations could explain variable phenotypic changes in DISC1 mouse model of complex gene-environment interactions consistent with symptom heterogeneity of schizophrenia.

4:00-6:00 **Symposium: A translational perspective on the neural circuitry of learning and decision making via positive and negative feedback.** Chairs: **Jonathan Brigman, Jared W. Young.** *Guttenberg Suite*

4:00 **Dopaminergic influence on learning via positive and negative feedback.** Jared W. Young, Jordy van Enkhuizen, Kerin Higa, Xianjin Zhou, Susan B. Powell, and Mark A. Geyer. Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, La Jolla, 92093-0804, USA. Background: Patients with neuropsychiatric disorders exhibit poorer learning, negatively impacting social and workplace environments as well as any benefit cognitive remediation might have for these patients. This impaired learning can be quantified using a probabilistic learning task. In-depth analyses of poor learning in patients reveals that deficits arise from poor decision-making in response to feedback, e.g. poor reward-associated learning in schizophrenia, hyposensitivity to punishment in bipolar disorder, and hypersensitivity to punishment in depression. Understanding the mechanism(s) underlying these aspects of probabilistic associative learning may aid in the development of treatments that can enhance learning, improving work placement and augmenting cognitive remediation. Dopamine is integral to the reward-error hypothesis of learning, thus we investigated its role in probabilistic learning and decision-making in response to feedback. Methods: By using pharmacological, genetic, and shRNA-viral techniques, we investigated what effect altering dopamine levels acutely, chronically, and removing some of their sites of action (respectively), would have on probabilistic learning in mice. Results: Mice with shRNA-induced suppression of striatal dopamine D1 receptors exhibited poorer learning as a result of poor reward-related learning (reduced maintenance of choice after a reward). Acute dopamine and norepinephrine transporter blockade via amphetamine administration enhanced learning in mice, primarily by improving reward-related learning. In contrast, mice that have chronically reduced dopamine transporter levels exhibited poorer learning due to a hyposensitivity to punishment (reduced shifting of choice after a punishment). Discussion: These studies support the hypotheses that striatal dopamine D1 suppression deleteriously affects reward-associations, acute hyperdopaminergia enhances reward-associations, and chronic hyperdopaminergia reduces sensitivity to punishment. Thus, dopamine plays a key role in learning under probabilistic contingencies. More importantly, differentially altering dopamine action affected learning by altering decision-making in response to feedback. Supported by National Institute of Mental Health Award (R01-MH071916; R21-MH081037), and the Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center.

4:30 **The representation of time, probability and uncertainty by mice.** Charles (Randy) Gallistel, Rutgers University, NJ, USA. In our switch paradigm, the mouse switches from poking into a short-latency feeding hopper to poking into a long-latency feeding hopper on those trials on which the short-latency hopper fails to deliver because the computer silently armed the long-latency hopper rather than the short-latency hopper. We record the switch latencies while manipulating the latencies, the variability in the latencies, and the probability that the computer will arm the long-latency hopper. From these data,w e can estimate how well a mouse can time and remember two different intervals, how well they represent their temporal uncertainty, how well and quickly they can estimate a Bernoulli probability, and their

ability to take all of these quantities into account in order to compute an approximately optimal target switch time. One recent surprise from this paradigm is that mice distinguish between external and internal (representational) sources of uncertainty (external variability versus lack of precision in their representation of single intervals).

5:00 **Prefrontal regulation of decision-making in a rat analogue of the Iowa Gambling Task.** van den Bos, R. Radboud University Nijmegen; Koot, S. Utrecht University; de Visser, L. University Medical Centre Utrecht. In 1994, the Iowa Gambling Task (IGT) was published by Damasio and colleagues (Damasio, Descartes' Error; Bechara et al., Cognition 50, 7-15). In this task subjects need to find the optimal solution for earning money in a context of variable wins and losses, conflicting short-term and long-term (dis)advantageous options, and uncertainty of outcomes. The IGT has revolutionized ideas on the role of the emotional system in the organisation of (decision-making) behaviour. In 2006, we published the first rodent version of the IGT (r-IGT; van den Bos et al., Behavior Research Methods 38, 470-478). This model allowed us to study brain-behaviour relationships underlying decision-making behaviour in rodents in more depth than would be possible in humans. We conducted most of our rodent studies in tandem with studies in humans to secure the translational value of our model. Here, we will review the results of our studies conducted over the past 7 years in which we have looked at the role of different prefrontal-subcortical circuits, including the role of serotonin and dopamine, in decision-making in male and female subjects. We will draw on published and hitherto unpublished material. Our studies have increased our understanding of how and why the interaction between emotion and cognitive control is crucial to navigate human and non-human animals alike through a world of variable wins and losses, conflicting short-term and long-term (dis)advantageous options, and uncertainty of outcomes.

5:30 **Updating expectation: Orbitfrontal cortex and flexible behavior.** Sigdel, R. Phillips, C.A., and Brigman, J.L., Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM. The uncontrolled continuation of a response when it is no longer beneficial, often referred to as maladaptive perseveration, is a common cognitive symptom of numerous neuropsychiatric disorders, including but not limited to schizophrenia obsessive compulsive disorder and addiction. Cognitive symptoms such as perseveration have become a major research focus as they can have wide impact on quality of life factors such as holding a job, managing finances and even maintaining personal relationships. One subregion of the prefrontal cortex, the orbitofrontal cortex (OFC) has extensive connections with subcortical associative learning areas such as the striatum, and has been strongly tied to the hallmark clinical and pre-clinical measure of perseveration: reversal learning. It has been hypothesized that the major role of OFC in cognitive flexibility is to signal the expected outcome of an action and, crucially, to detect when the expected outcome does not agree with what occurs, as in early reversal learning. Consistent with studies in primates and rats, we have recently shown that circuits connecting OFC and subcortical structures such as the striatum underlie learning and reversal of visual discriminations in mice. Evidence from both immediate early gene and OFC specific lesion has shown that that the region is selectively recruited during early, perseverative, reversal learning and that the area is functionally necessary for optimal visual reversal performance. We have also recently demonstrated the utility of integrating touch-screen visual learning paradigms with in vivo electrophysiological recording to examine firing rates and patterns during specific aspects of learning behavior (initiation of a trial, correct or incorrect response, reward retrieval) and examine how these variables change during specific time points. Here we have used these techniques to examine the organization of neuronal firing in the OFC as mice learn discriminative choice learning and, importantly, how firing changes during early, perseverative reversal. Our results showed event-related phasic neurons in the OFC as well as learning related changes in cortical firing patterns during initial discriminative learning and reversal performance. Taken together this data further supports the role of the OFC in monitoring outcome expectancies in changing environments and provides insight into how dysregulation of corticostrial networks may lead to cognitive deficits. Research supported by National Institute on Alcohol Abuse and Alcoholism grants 1K22AA020303-01 and P20-AA017068

6:00-8:00 **Break**

8:00-10:00 **Poster Session 3: Behavioral biology and development.** *Guttenberg Suite*

113. **The role of cingulate cortex regions in subjective time perception**. Kozlovskiy, S. Lomonosov Moscow State University, Moscow, Russia Pyasik, M. Lomonosov Moscow State University, Moscow, Russia Vartanov, A. Lomonosov Moscow State University, Moscow, Russia Nikonova, E. Lomonosov Moscow State University, Moscow, Russia. The role of cingulate cortex in time perception is still being discussed. Some studies demonstrate primary role of anterior cingulate cortex (ACC) in time perception (Mies, 2011; van der Veen, 2011), whereas the others revealed posterior cingulate cortex (PCC) involvement in this process (Hirono, 1998). We analyzed the relation between the sizes of different cingulate cortex regions and subjective time perception. Subjects: 25 right-handed females (mean age – 61 years old). We performed magnetic resonance morphometric analysis of T1 images in order to measure absolute square surfaces (in mm^2) of three cingulate cortex regions – anterior (BA 24), posterior (BA 23), and retrosplenial (BA 26, 29, 30; RCC) areas of both hemispheres. To assess subjective time perception we asked the subjects to estimate assessment duration and one minute interval. We calculated non-parametric correlations ($p < 0.05$) between individual behavioral and morphometrical data. We revealed positive correlations between subjective estimation of assessment duration and the sizes of ACC ($r=0.61$), PCC ($r=0.52$) and RCC ($r=0.43$) in the left hemisphere; subjective minute estimation correlates negatively with the

size of right RCC (r=-0.45). According to the results, subjective time perception is related to the left cingulate cortex functioning. The revealed correlations are higher for the ACC than for the PCC and also PCC size correlates with time perception better than RCC size. Thus, we revealed retrosplenial-rostral gradient of cingulate cortex involvement in subjective time perception.

114. **Induction of species-typical 50 kHz vocalizations by dopaminergic agents injected into the lateral septum in the rat**. Silkstone, M.; Brudzynski, S.M. Department of Psychology, Brock University, St. Catharines ON, Canada. The mesolimbic dopamine system has robust input into the nucleus accumbens. Dopaminergic agents, such as amphetamine or apomorphine, can induce 50 kHz vocalizations when injected directly into the shell of the nucleus accumbens in the rat. There is paucity of information regarding similar responses induced from other forebrain regions innervated by the mesolimbic dopamine system. The goal of the present study was to establish if dopaminergic agents could elicit ultrasonic vocalization from the lateral septum. Long Evans rats were stereotaxically implanted with chronic cannulae in septum for intracerebral injections in a volume of 0.3 µl. After recovery, rats were injecetd with R(-)-apomorphine hydrochloride (1-3 µg), (+-)-2-amino-6,7-dihydroxy-1,2,3,4-tetrahydro-naphtalene hydrobromide (ADTN, 0.5-10 µg) and saline as a control. Apomorphine dose-dependently increased the number of both flat and frequency-modulated (FM) 50 kHz vocalizations. There was on average 3.2 times more flat 50 kHz calls than FM 50 kHz calls after apomorphine. Similarly, ADTN dose-dependently increased the number of flat and FM 50 KHz calls, with 1.6-time more flat than FM 50 kHz vocalizations. Although, apomorphine was more potent in inducing 50 kHz calls, ADTN seemed to be more effective in inducing FM type of 50 kHz vocalizations than apomorphine. Supperted by the Natural Sciences and Engineering Research Council of Canada.

115. **Presynaptic CaMKII regulates short-term plasticity via syntaxin**. Michihiro Igarashi. Yumi Watanabe, Hirokazu Katayama, Toshiya Manabe, Keizo Takao, Tsuyoshi Miyakawa/1NIIgata Univ, 2Tokyo Univ, 3Fujita Hlth Univ, 4 NIPS of Japan. Ca2+/calmodulin-dependent protein kinase II (CaMKII) is an important modulator of neural plasticity. CaMKII is a major component of presynaptic terminals as well as postsynaptic densities; therefore, CaMKII probably mediates presynaptic plasticity via regulation of the exocytotic machinery. Previously, we found that autophosphorylated CaMKII interacts with syntaxin-1A to regulate exocytosis and that a syntaxin missense mutation [R151G] attenuated this interaction. To more precisely analyze the physiological importance of this interaction, we generated mice with a knock-in (KI) syntaxin-1A [R151G] mutation. These KI mice exhibited abnormal presynaptic plasticity, and had a more pronounced synaptic response than did wild-type (WT) littermates, which included a behavioral abnormality; these R151G phenotypes are generally consistent with the previously reported phenotypes of CaMKII mutant mice. The KI mice exhibited locomotor hyperactivity in the open field and fewer anxiety-like behaviors. Contextual memory tests revealed that the KI mice showed less freezing less freezing following conditioning. In the Porsolt forced swim test, the KI mice traveled longer distance than did WT mice on the first day, and displayed decreased immobility on the following day. The KI mice showed performance deficit in the initial phase of training of the eight-arm radial maze test, which is a test that assess working memory. Base on all these findings, the KI mice, which have only a single point mutation (syntaxin-1A [R151G]), showed disorders of several higher brain functions. In particular, like CaMKII□+/- mice, the KI mice showed hyperactivity, decreased anxiety-like behaviors, decreased depression-like behavior, and impairment of working memory; these findings indicate that the R151G mutation causes insufficient CaMKII action in the presynaptic terminal. These results indicated that presynaptic CaMKII plays an important role in short-term plasticity by physiologically inhibiting the excess neurotransmission caused by frequent stimuli.

116. **Mitragynine impaired one-trial inhibitory avoidance task in rats**. Farah Wahida Suhaimi1, Zurina Hassan1, Visweswaran Navaratnam 1, Christian P. Müller2 1Centre for Drug Research, Universiti Sains Malaysia, Penang, Malaysia. 2Psychiatrische und Psychotherapeutische Klinik, Universitats Klinikum Erlangen, Friedrich-Alexander-Universitat Erlangen- Nurberg, Erlangen, Germany. Mitragynine, the major alkaloid constituent extracted from Mitragyna speciosa Korth from Rubiaceae family has been widely used throughout Southeast Asian countries. The leaves of M. speciosa, also known as ‘kratom’ in Thailand and ‘ketum’ or ‘biak-biak’ in Malaysia, are often chewed, smoked or taken as tea and has been traditionally used as a substitutes for opium, to increase work efficiency and to reduce pain sensitivity. However, scientific information on cognitive functions particularly learning and memory is limited. In this study, acute effects of mitragynine on acquisition, memory consolidation and retrieval of inhibitory avoidance task were investigated. Male Sprague-Dawley rats (180-250 g) were intraperitoneally administered with mitragynine (1, 5 or 10 mg/kg) before training, immediately after training or before test, respectively. Rats were trained with single exposure to footshock (0.5mA, 10 s) and step-through latency (s) was taken as a measure of retention score. Results showed significant reduction in step-through latency in mitragynine-treated groups against vehicle-treated group regardless of their doses. No significant difference was observed in mitragynine-treated groups versus morphine-treated group (5 mg/kg). The reduction in step-through latency was similar in acquisition, consolidation and retrieval process. Results obtained suggest that mitragynine does impair the learning and memory process in one-trial inhibitory avoidance task in rats.

117. **Noradrenergic transmission enhancement during memory consolidation and reconsolidation induces fear generalization as a matter of contextual conditioning intensity in rats.** Gazarini, L. Departamento de Farmacologia, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Florianópolis/SC. Stern, CAJ. Departamento de Farmacologia, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Florianópolis/SC. Carobrez, AP. Departamento de Farmacologia, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Florianópolis/SC. Bertoglio, LB. Departamento de Farmacologia, Centro de Ciências Biológicas, Universidade Federal de Santa Catarina, Florianópolis/SC. Fear generalization is a posttraumatic stress disorder (PTSD) feature that could result from inappropriate memory processing. Since PTSD is associated with adrenergic hyperactivity, we investigated the ability of yohimbine (YOH; 1.0 mg/kg, i.p.), an α2-adrenoceptor antagonist that enhances noradrenergic transmission, to induce fear generalization when given immediately after acquiring (consolidation) and/or retrieving (reconsolidation) a contextual fear memory. To this aim, male Wistar rats were subjected to the following protocol: 1) Context A familiarization; 2) Context A pairing with 1 or 3 (weak or strong training) foot-shocks (0.7 mA/3s); 3) fear memory retrieval/reactivation in Context A; 4) Context A re-exposure for fear memory inference (test A); and 5) exposure to a neutral context (test B), to evaluate the generalization occurrence. With the strong training, a single YOH administration during memory consolidation or reconsolidation was able to induce fear generalization, characterized by a robust freezing response relative to controls during test B. In the weak pairing protocol, a single YOH administration potentiated fear memory consolidation or reconsolidation, increasing freezing levels during test A, but only the repeated administration of YOH during consolidation and reconsolidation was able to induce fear generalization. Altogether, it is suggested that the aversiveness elicited by the contextual fear conditioning protocol influences the ability of noradrenergic hyperactivity to induce fear generalization.

118. **Morphological effects of memory erasure and disruption of memory reconsolidation in Aplysia californica.** Glanzman, D.L.[1,2,3,4]; Chen, S.[1].; Cai, D. [1]; Sun, P. [1] [1]IBP; [2]Neurobiol.; [3]ICLM; [4]BRI, University of California, Los Angeles, CA USA. To address the issue of whether the apparent absence of memory following inhibition of the catalytic fragment of atypical protein kinase C, PKMζ (Sacktor, 2011), or treatment with an inhibitor of memory consolidation following memory reactivation (Nader et al., 2000), reflects the actual erasure of the physical memory trace or, rather, a retrieval impairment, we studied these phenomena in a simple system, the marine snail Aplysia. Repeated, spaced delivery of electrical shocks to tail of Aplysia produces long-term sensitization (LTS) of the animal's defensive withdrawal reflex. LTS is accompanied by long-term facilitation (LTF) of the monosynaptic connection between the sensory and memory neurons that mediate the withdrawal reflex; moreover, LTF can be induced in sensorimotor cocultures by treatment with serotonin (5-HT). We have previously reported that inhibition of the Aplysia homolog of PKMζ, PKM Apl III (Bougie et al., 2009, 2012), appears to erase consolidated LTS, as well as consolidated LTF of sensorimotor synapses in coculture (Cai et al., 2011). Furthermore, both LTS and LTS exhibit reconsolidation (Cai et al., 2012; Lee et al., 2012). Here, we report that inhibition of PKM Apl III reverses the growth of new presynaptic varicosities that is induced during LTF; moreover, this long-term, learning-related morphological growth is also reversed when anisomycin, a protein synthesis inhibitor, is applied to sensorimotor cocultures immediately after reactivation of long-term synaptic memory. Together, these results provide unambiguous evidence that the phenomena of memory erasure and blockade of memory reconsolidation involve erasure of the stored memory trace. Support: NINDS and NIMH

119. **Hypothermia, bradycardia and regional c-Fos expression induced by peripheral oxytocin: Evidence for vasopressin 1A receptor involvement.** Callum Hicks[1], Linnet Ramos[1], Glenn E. Hunt[2], William Jorgensen[3], Bruno Dampney[1], Giti H. Misagh, Michael Kassiou[3] and Iain S. McGregor[1] [1]School of Psychology, Brennan MacCallum Building, University of Sydney, Sydney, NSW 2006, Australia; [2]Discipline of Psychiatry, Sydney Medical School, University of Sydney, Concord Hospital, NSW 2139, Australia; [3]Brain and Mind Research Institute, University of Sydney, Sydney, NSW 2050, Australia. Interest in oxytocin as a potential treatment for psychiatric disorders (e.g. autism) may be hindered by its poor blood-brain barrier penetration and significant cardiovascular and other peripheral side effects. Oxytocin also displays substantial affinity for the vasopressin 1A receptor ($V_{1A}R$), although the extent to which its functional effects are mediated by this receptor relative to the oxytocin receptor (OTR) is unclear. Here we used biotelemetry in freely moving rats to characterise the effects of oxytocin on body temperature and heart rate, and used a pharmacological approach to assess the involvement of the central and peripheral $V_{1A}R$ in these effects. Male Wistar rats were assessed after peripheral (0.01 - 1 mg/kg, IP) and central (0.1 - 1 µg/5 µL, ICV) oxytocin administration, and the ability of the $V_{1A}R$ antagonist SR49059 (1 and 10 mg/kg, IP) to prevent the physiological effects of peripheral oxytocin was determined. The non-peptide OTR ligand WAY 267,464 (10 and 100 mg/kg, IP) was also administered alone, or in combination with oxytocin (1 mg/kg, IP). A second study examined a possible interaction between oxytocin and the $V_{1A}R$ on neuronal activation using c-Fos immunohistochemistry. Rats were given oxytocin (1 mg/kg, IP) alone, or following pre-treatment with SR49059 (1 mg/kg, IP), and assessed for locomotor activity changes and regional c-Fos expression in the brain. Peripheral oxytocin at 1 mg/kg caused a strong hypothermic and bradycardic effect, and these were completely prevented by either dose of SR49059. Interestingly, however, centrally administered oxytocin had no effects on body temperature or heart rate at any of the doses tested. WAY 267,464 (100 mg/kg) decreased body temperature, similar to oxytocin, but had no effect on heart rate. Somewhat surprisingly, WAY 267,464 partially

attenuated the bradycardia caused by peripheral oxytocin. In the second study, SR49059 completely prevented oxytocin-induced locomotor hypoactivity and c-Fos expression in several regions, including the median preoptic nucleus, nucleus of the solitary tract and paraventricular hypothalamic nucleus. Peripheral V_{1A}R's may therefore underlie the strong hypothermic and bradycardic effects of peripheral oxytocin. The V_{1A}R, rather than the OTR, may also mediate oxytocin-induced neuronal activation in many behaviourally relevant brain regions. The current findings add to an increasing body of research that shows many of the functional effects of oxytocin to be V_{1A}R mediated.

120. **MK-801, but not Ifenprodil, disrupts fear expression and extinction**. B.L. Thomas, C. Novak, M. Hanna and M. Harakas. Baldwin Wallace University, Berea, OH, USA. The aim of this study was to compare the effects of MK-801 and Ifenprodil on explicitly unpaired (EU) extinction and renewal of fear. Using a conditioned suppression task, five groups of rats were given CS-US conditioning in Context A, either conventional (CS only) or EU (CS and US unpaired) extinction in Context A or B and were then tested for renewal of fear in Context A. Two groups were injected with either MK-801 or Ifenprodil prior to the start of each extinction session. Results showed that MK-801, but not Ifenprodil, disrupted fear expression during extinction and increased fear renewal. These findings suggest that selectively antagonizing NMDA receptors that contain the NR2B subunit did not alter the normal course of extinction or fear renewal. In Contrast, MK-801, a non-competitive antagonist, prevented fear expression, reduced fear extinction and increased fear renewal.

121. **Age-dependent differences in the persistence of cocaine-induced conditioned activity in adult and young rats: Regional differences in Fos immunoreactivity**. Sanders A. McDougall, Joseph A. Pipkin, Taleen Der-Ghazarian, Anthony M. Cortez, Arnold Gutierrez, Ryan J. Lee, Sandra M. Carbajal, Jena L. Shaddox, and Cynthia A. Crawford; Department of Psychology, California State University, San Bernardino, CA 92407. The neural mechanisms mediating conditioned activity (CA) are poorly understood, although the nucleus accumbens (NAcc), amygdala, and hippocampus have been implicated. In a typical experimental design, adult rats are given 4 to 8 cocaine-environment pairings before assessment of CA; however, rats will also show CA when a single injection of cocaine is given in a novel chamber 24 h before testing. The purpose of this study was to: (a) determine the persistence of one-trial CA in young and adult rats and (b) assess neural activation by measuring Fos IR. To that end, rats were injected with 30 mg/kg cocaine in a novel chamber or the home cage on postnatal day 19 or 79 (control rats were injected with saline in both contexts). For adult rats, CA was assessed 1, 3, 5, 7, 14, or 21 days later; whereas, young rats were assessed 1, 14, or 21 days after cocaine or saline treatment. Brains were removed after testing and processed for Fos IR. Young rats did not exhibit CA when tested 1, 14, or 21 days after a single cocaine-environment pairing. In contrast, adult rats showed robust one-trial CA that persisted for at least 21 days after cocaine treatment. CA was entirely context-dependent and did not occur if cocaine was given in the home cage. When assessed after 1 day, adult rats injected with cocaine in the novel chamber exhibited elevated Fos IR in the NAcc core and shell. Young rats as well as adult rats injected with cocaine in the home cage did not exhibit elevated Fos IR. These results indicate that a single drug-environment pairing is sufficient to induce long-term CA and that the NAcc may be involved in the induction and/or initial expression of CA. It also appears that a single drug-environment pairing is insufficient to induce CA in young rats. [Funded by NIH grant DA027985]

122. **A familiar conspecific is more effective in social buffering of conditioned fear responses in male rats**. Kiyokawa, Y.; Honda, A.; Takeuchi, Y.; Mori, Y. Laboratory of Veterinary Ethology, The University of Tokyo, Tokyo 113-8657 JAPAN. In the social buffering, a phenomenon known in various species, stress responses are less distinct when an animal is exposed to a stressor with one or more conspecific animals. The efficacy of social buffering is affected by several factors such as the number of conspecifics or stress level of the conspecific. However, it remains unclear how the familiarity influences the social buffering. We have previously found in male rats that olfactory signals from an unfamiliar male (associate) mitigate conditioned fear responses to an auditory conditioned stimulus (CS). Using this experimental model, we examined whether the familiarity of an associate influenced the efficacy of social buffering. We prepared familiar associates by keeping the associate with the subject in the same cage for 3 weeks whereas the subjects had not met with unfamiliar associates. On the test day, either familiar or unfamiliar associate was kept in the test box for 2 hours to leave its scent. After removing the associate, we placed the fear-conditioned subject in one of these two boxes and presented the CS. When the subjects were tested in the non-scented clean test box, they showed conditioned fear responses including freezing and increased Fos expression in the paraventricular nucleus (PVN). The olfactory signals from the unfamiliar associate blocked freezing and increment of Fos expression in the PVN. The subjects showed further reduction of freezing when it was tested in the test box scented by the familiar associate. However, the Fos expression in the PVN was not different between the familiar and unfamiliar associate groups possibly due to the floor effect. These results suggest that a familiar conspecific is more effective in social buffering of conditioned fear responses.

123. **Relief conditioning: Behavioral characterization and neural basis**. Markus Fendt, Institute for Pharmacology and Toxicology, Otto-von-Guericke University Magdeburg, Germany. During Pavlovian fear conditioning, stimuli predicting aversive events are learned as fear stimuli. This means that later such stimuli alone are able to induce fear which involves physiological and behavioral changes preparing animals or humans for further aversive

events. Fear learning is best when the to-be-learned stimulus immediately precedes the aversive event. However, what happens if the to-be-learned stimulus follows the aversive event, in the moment of relief? Studies in Drosophila demonstrated that such a stimulus can also be learned. However, the stimulus does later not induce fear responses like avoidance behavior but appetitive responses like approach behavior. This phenomenon was called relief conditioning. Here, first studies on relief conditioning in rats are presented. First, we developed a protocol for relief conditioning. As a behavioral measure, we used the acoustic startle response. If during conditioning a light stimulus was presented in a particular time window after an aversive stimulus, this light stimulus later induced a significant attenuation of the startle magnitude which is regarded as an appetitive response. If the light stimulus is presented later or randomly, only a weak startle attenuation was measured which we interpreted as safety conditioning. Presentation of the light stimulus before the aversive stimulus induced – as expected – fear conditioning. Then, the role of the amygdala and the nucleus accumbens in relief conditioning was investigated. In rats, either the amygdala or the nucleus accumbens were temporally inactivated (by local injections of the GABA-A receptor agonist muscimol) and the animals were tested for conditioned relief or conditioned fear, respectively. Inactivation of the nucleus accumbens but not of the amygdala blocked the expression of conditioned relief. In contrast, inactivation of the amygdala blocked conditioned fear without affecting conditioned relief. This neural dissociation was also found in humans by fMRI studies. Thus the behaviorally opponent memories supported by the onset and the offset of aversive events are mediated by different neural substrates. Currently, we are investigating the stability of conditioned relief and the involved transmitter systems.

124. **Temporal object memory in mice and the role of histamine 1 receptor**. Armin Zlomuzica[1,2]; Ekrem Dere[2,3] [1]Mental Health Research and Treatment Center, Bochum, Germany; [2]Institute of Experimental Psychology, University of Düsseldorf, Germany; [3]UMR 7102, Neurobiologie des Processus Adaptatifs, Université Pierre et Marie Curie, Paris 6, Paris, France. Over the past decade, we have provided evidence that rodents show episodic-like memory, i.e. that they are able to remember previous experiences with respect to their content and their temporal and spatial contexts. We also demonstrated that the genetic inactivation of histamine 1 receptor (H1R) in mice impairs episodic-like memory, yet the exact nature of this impairment requires further investigation. A core component of human episodic memory is the ability to encode and retrieve the temporal order of unique events. There are only few experimental paradigms available which can be used to investigate the temporal component of episodic memories in animals. The aim of this study was to clarify whether the animals' memory performance in the temporal order memory (TOM) task is guided by either recollection or familiarity based processes and whether the H1R mediates TOM in mice. According to the dual process model of recognition, recollection is less susceptible to delay dependent forgetting than familiarity. This argues for a difference in the temporal dynamics of recollection and familiarity based retrieval. Based on this general idea of the dual process model, we tested whether the experimental manipulation of the inter-trial intervals in the TOM task leads to changes in TOM performance. We hypothesized that familiarity-based performance should be modulated by the reduction of the delay between to events, while recollection-based performance should be unaffected by changes of the inter-trial or inter-event interval. Our results suggest that the reduction of the inter-trial or inter-event-interval has no detrimental effect on TOM performance in the mouse. However, H1R deficient mice showed impaired TOM when being tested under both, short- and longer inter-trial intervals. Our results point to a recollection-based recognition performance in the TOM task in mice. Furthermore, our results suggest an important role of H1 receptor in TOM as a critical component for the demonstration of intact episodic-like memory in mice.

125. **T-type Ca2+ channels, Cav3.1, in GABAergic neurons of the medial septum are critical in regulation of hippocampal theta oscillations and behavior response to novelty.** Gireesh Gangadharan and Hee-Sup Shin Center for Cognition and Sociality, Institute for Basic Science Daejeon 305-811, Republic of Korea. Knock-out mice for the T-type calcium channel, Cav3.1, show multiple behavioral phenotypes including decreased anxiety, locomotive hyperactivity, and increased behavior response to novelty. We have carried out experiments to identify the neural substrates for the complex phenotypes. The mutant mice showed enhanced hippocampal theta oscillations. Cav3.1 T-type channels are strongly expressed in GABAergic neurons in the medial septum which is known to drive hippocampal theta oscillations. Importantly, medial septal-specific knockdown of Cav3.1 induced enhancements of hippocampal theta oscillations and novelty behavior. Interestingly, the knockdown mice showed normal levels of anxiety and locomotive activity, suggesting that the modulation of theta oscillations by septal T-type channels is specifically linked to the novelty behavior. Finally we found that the septo-hippocampal projecting GABAergic neurons deleted for T-type channels showed markedly increased tonic firing activity, which could be responsible for the enhancement of hippocampal theta oscillation. These results highlight a critical role of Cav3.1 T-type calcium channels of the medial septum in control of hippocampal theta oscillations and novelty behavior.

126. **The rapid effects of the G-protein coupled estrogen receptor in the hippocampus on learning and memory in female mice**. Lymer, J., Gabor, C., Phan, A., Magahay, A., Baines, N., Choleris, E.; University of Guelph. Estrogens have been proven to rapidly affect learning and memory processes in mice (Phan et al., 2011; 2012). A recently discovered estrogen receptor, the G-protein coupled estrogen receptor (GPER) has been implicated in the rapid effects of estrogens on learning and memory processes such as social recognition, object recognition, and

object placement. Systemic treatment of the GPER agonist G-1 has been shown to rapidly improve performance in these learning paradigms in ovariectomized female mice. Furthermore, a recent study has demonstrated that intrahippocampal infusion of 17-beta estradiol has a similar effect in ovariectomized female mice. GPER in the hippocampus may mediate these improving effects. This study investigates the rapid effects of G-1 (50, 100, 200, 300, or 400 nM) infusions (rate of 0.2 μL/min for a total volume of 0.5 μL per side) in the hippocampus on social recognition, object recognition, and object placement in ovariectomized female mice. The paradigms to test these learning and memory tasks are completed within 40 minutes of drug administration and therefore focus on the rapid, non-genomic effects of GPER within the hippocampus. Intrahippocampal infusion of the 200 nM G-1 dose improved social recognition and infusion of the 100 nM G-1 dose significantly improved object placement. Experiments testing intrahippocampal G-1 effects on object recognition are currently underway. These results suggest that GPER in the hippocampus may, in part, mediate the rapid, improving effects of estrogens on social recognition and object placement in female mice. Supported by NSERC.

127. **Non-genomic enhancing effects of estrogens on learning are mediated through ERα in the hippocampus**. Phan A1, Suschkov S2, Molinaro LP2, MacLusky NJ2, Choleris E1 1Dept of Psychology, 2Biomedical Sciences, University of Guelph, Guelph, ON, Canada. We recently demonstrated low doses of systemic 17β-estradiol rapidly improved social recognition, object recognition and object placement learning in ovariectomized mice within 40min of treatment (Phan et al., 2012. Neuropsychopharm, 37:2299). The estrogen receptor (ER)α agonist PPT mimicked the effects of 17β-estradiol, while ERβ agonist DPN only improved object placement learning (Phan et al., 2011. Endocrinology, 152:1492). Therefore, this rapid and likely non-genomic effect appears to be mediated through ERα. In addition, systemic administration of 17β-estradiol and PPT increased CA1 hippocampal dendritic spine density, while DPN had no effect or decreased spine density. Thus, the increased synaptic density within the hippocampus may facilitate the rapid effects of estradiol on learning. To determine the role of the hippocampus for this effect, we microinfused 0.5μL (per hemisphere) of vehicle, 17β-estradiol (25, 50, 100nM), PPT or DPN (50, 100, 150nM), into the hippocampus of CD1 ovariectomized female mice, 15min prior to testing social recognition, object recognition and object placement performance in home cage. Paradigms were completed within 40min. We found that intrahippocampal delivery of 50nM 17β-estradiol and of 100 and 150nM PPT improved performance on all 3 learning paradigms, while intrahippocampal administration of 100nM DPN improved object placement learning only. Therefore, the hippocampus can mediate the non-genomic enhancement of estrogens on learning, apparently through an ERα mechanism. Funded by NSERC.

128. **Estrogen receptor agonists have rapid and differential effects on social learning in female mice**. Ervin, K.; Mulvale, E.; Boyd, J.; Montini, G.; Melendez, A.; Choleris, E. Dept. of Psychology, University of Guelph, Guelph, ON N1G 2W1 Canada. Through social learning animals acquire information from conspecifics. In the social transmission of food preferences (STFP), an observer mouse learns about a novel flavoured food it smells on the breath of a conspecific demonstrator and subsequently prefers that food. Estrogens affect STFP via both long-term, genomic mechanisms and rapid, non-genomic mechanisms. On a long-term time scale, estrogen receptor (ER) beta agonists improve performance, while ER-alpha agonists block the preference (Clipperton et al., 2008). We examined the rapid effects focusing on the first hour after hormone treatment and modifying the STFP paradigm to differentiate impairing or improving treatment effects. In an "easy" version, control animals readily learn, and in a "difficult" version, controls show no learning. We previously found that 17beta-estradiol rapidly improved learning on the "difficult" STFP paradigm. Here we administered selective ER agonists subcutaneously to the observer mouse 15 minutes prior to social interaction to investigate the rapid involvement of ER-alpha, ER-beta, and the recently described G-protein coupled ER (GPER1) in the STFP. We administered 30, 50, 75, and 150ug per mouse of the ER-alpha agonist propyl pyrazole triol (PPT), and the ER-beta agonist diarylpropionitrile (DPN), and 30, 90, 180, and 900ug of the GPER1 agonist G1. Consistent with its long-term effects, ER-alpha agonist PPT (30ug) blocked STFP in the "easy" task. Unlike the long-term effects, the ER-beta agonist DPN did not improve social learning in the "difficult" paradigm. Mice treated with GPER1 agonist G1 (180ug) showed improved social learning on the "difficult" STFP paradigm, similar to 17beta-estradiol. It therefore seems that GPER1 may mediate the rapid improving effects of 17beta-estradiol, and that the impairing effects of ER-alpha on social learning occur on both the rapid and long-term/genomic time scale. Funded by a grant from the Natural Sciences and Engineering Research Council of Canada (NSERC)

129. **Dopamine and memory: Involvement of hippocampal dopamine D1-type receptor in the social transmission of food preferences in male and female mice**. Matta, R., Tiessen, A. N., & Choleris, E. Dept. of Psychology, University of Guelph, Guelph, ON N1G 2W1 Canada. The neurotransmitter dopamine plays a fundamental role in a wide variety of behaviors, including social interactions, social learning, food intake, and memory processes. Our past systemic work has implicated the involvement of the dopamine D1-type receptor in social learning (Choleris et al., 2011); however, the exact brain regions of such action remain unknown. Dopaminergic mesencephalic neurons in the ventral tegmental area project to numerous limbic structures, including the hippocampus, a structure essential for the social transmission of food preferences (STFP) memory task. Hence, we wanted to determine whether the D1-type receptor in the CA1 region of the dorsal hippocampus mediates responses to environmental stimuli of a social nature. To do this (in an on-going study), we are microinfusing the D1-type receptor antagonist,

SCH23390 (1, 2, 4, and 6 μg/mouse), into the hippocampus of adult male (n = 16) and female (n = 15) CD-1 mice 15 minutes prior to a 30 minute social interaction during which mice acquire a food preference from a conspecific. This examination of the interplay between the hippocampus and memory may reveal one likely brain site underlying dopamine's contribution to acquiring social information. Taking into account the established regulation of the dopaminergic system by sex hormones, and the influence of estrogens on social learning, our study will also highlight possible sex differences in learning and memory driven by dopamine. Supported by NSERC.

130. **Differential role of glutamatergic mechanisms of the medial hypothalamus on the expression of unconditioned and conditioned fear responses**. Reimer, A.E.; de Oliveira, A.R.; Brandão, M.L. Universidade de São Paulo, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, SP, Brasil; Instituto de Neurociências e Comportamento, Ribeirão Preto, SP, Brasil. The medial hypothalamus (MH) is a brain structure involved with the integration of endocrine, autonomic and behavioral responses. In rats, the electrical stimulation of the MH produces a series of behavioral responses that resemble those defensive responses triggered in the presence of a predator. Some evidence points to an involvement of glutamatergic mechanisms in the defensive responses generated at MH level. The objective of the present study was to evaluate the involvement of glutamatergic mechanisms of two MH nuclei – the anterior nucleus (AH) and the dorsal pre-mammillary nucleus (PMd) – in the expression of unconditioned and conditioned fear responses. To this end, we evaluated the effects of glutamatergic agonists and antagonists (AMPA/Kainate and NMDA) administered into these nuclei in the open-field test and in the fear potentiated startle and conditioned freezing responses to a light conditioned stimulus (CS). In the open-field test, the administration of glutamatergic agonists, in both AH and PMd, produced an increase in locomotion and infrequent but coordinated jumps toward the arena walls. Glutamatergic antagonists increased locomotion but compromised animals' motor skills, increasing the number of rotations and falls. The administration of glutamatergic agonists and antagonists into AH and PMd, in doses that did not cause unconditioned defensive responses, produced no significant effects on the conditioned fear responses evaluated here. The present results suggest the involvement of MH glutamatergic mechanisms mediated by AMPA/Kainate and NMDA receptors in the expression of unconditioned fear responses but not in expression of conditioned fear responses to a light-CS. Financial support CNPq. Travel grant: IBRO.

131. **Mineralocorticoid receptors in the ventral tegmental area regulate dopamine efflux in the basolateral amygdala during the expression of conditioned fear**. de Oliveira, A.R.; Reimer, A.E.; Brandão, M.L. Universidade de São Paulo - Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, SP, Brasil; Instituto de Neurociências e Comportamento - INeC, Ribeirão Preto, SP, Brasil. Dopamine (DA) is released in the basolateral amygdala (BLA) from the ventral tegmental area (VTA) during the expression of conditioned fear. However, the mechanism by which a conditioned stimulus (CS) increases DA efflux in the BLA remains to be determined. The activation of the hypothalamic-pituitary-adrenocortical axis, reflected by an increase in plasma corticosterone in rodents, has been considered a key part of the stress reaction. Corticosterone activates two types of receptors: mineralocorticoid (MR) and glucocorticoid (GR), both present in the VTA and BLA. Therefore, some aspects of the stress reaction may occur via changes in DA levels subsequent to the binding of corticosterone to these receptors. The present study sought to clarify the involvement of MRs and GRs of the VTA and BLA on the expression of conditioned freezing and release of DA in the BLA. The first experiment assessed the effects of intra-VTA or intra-BLA spironolactone (MR antagonist) or mifepristone (GR antagonist) on the expression of conditioned freezing to a light-CS and motor performance in the open-field test. Intra-VTA spironolactone, but not mifepristone, attenuated the expression of conditioned freezing response. Intra-BLA spironolactone or mifepristone had no significant effects. The drugs did not affect motor performance in the open-field test. In the second experiment, we used in vivo microdialysis to investigate the role of VTA MRs in mediating the effects of CS on DA efflux in the BLA. We demonstrate that blocking MRs locally within the VTA with spironolactone results in a reduction in DA efflux in the BLA and a decrease in the expression of conditioned freezing in response to the CS. Taken together, these data indicate that during the expression of conditioned fear to a light-CS corticosterone acts locally at MRs within the VTA to stimulate DA efflux in the BLA. Financial Support: FAPESP.

132. **Non genomic effects of corticosterone influence fos protein expression in the prefrontal cortex and expression of contextual fear conditioning in rats.** Reis, FMCV 1,3; Almada, RC 1,3; Fogaça, MV 2,3; Brandão, ML 1,3. 1 Laboratory of Neuropsychopharmacology, Dept. of Psychology - FFCLRP, 2 Dept. of Pharmacology – FMRP, University of Sao Paulo, 3 Instituto de Neurociências & Comportamento - INeC, – Ribeirao Preto, SP, Brazil. Recently it has been given emphasis on role of the medial prefrontal cortex (mPFC) in processes related to aversive conditioning. Acute changes on circulating corticosterone concentrations can influence emotional behaviors through different activation of mineralocorticoid (MR) or glucocorticoid receptors (GR). The mPFC has been implicated on the modulation of endocrine and defensive responses although little is known about how the rapid effects of glucocorticoids in this region may influence the expression of conditioned fear. The present study investigated the effects of metyrapone, a corticosterone synthesis blocker, on freezing response of rats subjected to contextual fear conditioning as well as the involvement of different mPFC subregions in this response by analysis of Fos-protein expression. Additionally, the effects of combined administration of

GR/MR antagonists into the mPFC on freezing response were also evaluated. Wistar male rats received either vehicle or metyrapone (30mg/kg) and were exposed to a context previously paired with footshocks. The results showed that exposure of rats to the aversive context led to increased freezing and Fos-protein expression in the prelimbic cortex (PrL) and anterior cingulate areas 1 and 2 (Cg1/Cg2). Furthermore, metyrapone administration decreased freezing and Fos expression in the PrL, Cg1 and Cg2. The administration of the MR antagonist into the PrL also reduced freezing expression while the GR antagonist produced no effects. Previous administration of GR antagonist into the PrL abolished the anxiolytic effects of MR antagonist in this region. Overall, the present data showed that the mPFC is involved on the expression of contextual conditioned fear, highlighting the importance of the PrL subregion. The modulation of conditioned fear in the PrL is partly influenced by an interaction between mechanisms mediated by MR/GR receptors so that the anxiolytic effects produced by MR antagonism may be due to the displacement of corticosterone to the lower affinity GR receptors. Financial support: FAPESP/IBRO.

133. **Heparan sulfate deficiency in autistic postmortem brain tissue from the subventricular zone of the lateral ventricles.** Corley, MJ, Pacific Biosciences Research Center, University of Hawaii, Honolulu, HI, 96822, USA. Pearson, BL, Department of Cell Biology and Physiology, University of North Carolina, 115 Mason Farm Road, Chapel Hill, NC 27599, USA Vasconcellos, A, Pacific Biosciences Research Center, University of Hawaii, Honolulu, HI, 96822, USA. Blanchard, DC, Pacific Biosciences Research Center, University of Hawaii, Honolulu, HI, 96822, USA. Blanchard, RJ, Pacific Biosciences Research Center, University of Hawaii, Honolulu, HI, 96822, USA. Abnormal cellular growth and organization in the brain have been characterized as neuropathological features of autism, suggestive of pathology in a critical developmental neurogenic niche, the subventricular zone (SVZ) of the brain lateral ventricles (LV). However, human studies of autism utilizing postmortem brain tissue have not yet studied the LV-SVZ region. Therefore, we examined the LV-SVZ of young to elderly individuals with autism (n = 4) and age-matched typically developing (TD) individuals (n = 4) using immunofluorescence techniques. We assessed cellular organization, proliferation, and a critical component of the LV-SVZ extracellular matrix [N-sulfated heparan sulfate (HS)]. The LV-SVZ of autism and TD samples was characterized by a similar unique 4-layered cellular organization consisting of an ependymal wall, hypocellular gap, astrocytic ribbon, and transitional layer. For young through mature, but not elderly, autistic pair members, the distribution and magnitude of HS in the LV-SVZ was significantly reduced compared to matched TD individuals. Cellular proliferation (Ki67+ cells) in the LV-SVZ was higher in the autistic individual of the youngest age-matched pair. These preliminary data suggesting that HS may be reduced in young to mature autistic individuals are in agreement with previous findings from the BTBR T+tf/J mouse, an animal model of autism; from mice with genetic modifications reducing HS; and with genetic variants in HS-related genes in autism. They suggest that aberrant extracellular matrix glycosaminoglycan function localized to the LV-SVZ may be a biomarker for autism, and potentially involved in the etiology of the disorder.

134. **Male monkeys (Cebuslibidinosus) behave differently according to the hormonal fluctuations of female reproductive cycle?** Rodrigues, R.C.1; Gasbarri. A.2; Tomaz, C.1;Tavares, M.C.H1* 1 Primate Center and Laboratory of Neurosciences & Behavior, University of Brasília, Brasília, DF, Brazil. cDepartment of Sciences and Biomedical Technologies, University of L'Aquila, L'Aquila, Italy. The present study aimed to evaluate behavioral and hormonal aspects of Cebus libidinosus kept in the Primate Center at the University of Brasilia (UnB). Sexual and non-sexual behaviors of three adult monkey couples were monitored during 60 days. Fecal material was collected to measurements of progesterone, estradiol (female) and testosterone (males) sex hormonal profiles. Behavior observation used the focal animal method with continuous records (7 minutes) and snapshots (range of 15 seconds during 7 minutes) three times per week per animal. Hormonal extraction in fecal samples occurred by hydrolysis and solvolysis. ELISA (immunoenzymatic technique) was used for the hormone dosages. The results revealed significant differences in sexual behavior of females throughout menstrual cycle, where the highest expression occurred in follicular phase ($p \leq 0.05$). There were no significant differences of behavior expression of males towards female cycle phases. This refutes the hypothesis that these males behave differently due to the hormonal fluctuations of female reproductive cycle. However, in hormonal terms, progesterone levels varied throughout the cycle between 0.01 and 99 ng/g feces, and estradiol levels were between 0.01 and 900 ng/g. Males showed testosterone levels between 0.01 and 351 ng/g feces. It was observed a synchrony between male testosterone levels and the female menstrual cycle, which may indicate that sexual cues emitted by females are perceived by males of somehow. Possibly these behavioral cues could also act on chemical signals between these animals, which could have contributed to the synchronization of sex hormones.

135. **Bed nucleus of the stria terminalis CRF1, but not CRF2, receptors mediate the expression of contextual fear conditioning.** Hott, S.C.; Gomes, F.V.; Uliana, D.L.M.; Resstel, L.B.M. Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto-SP, Brazil. The bed nucleus of the stria terminalis (BNST) is involved in the expression of anxiety-like responses, including conditioned emotional responses (CER). It contains a large number of neurons expressing corticotrophin releasing factor (CRF), and evidence suggests an increase of the level of this neuropeptide during aversive situations. Previous studies showed the involvement of the BNST in stress responses mediated by CRF1 receptors (CRFR1). Thus, we investigated the involvement of the BNST CRFergic system in the modulation of the CER induced by contextual fear conditioning

(CFC) in rats. Male Wistar rats (240-270g) with cannulae implanted bilaterally into the BNST were submitted to a 10min conditioning session (3 footshocks, 0,85mA, 2s-low intensity or 6 footshocks, 1,5mA, 3s-high intensity). 24h later, the behavioral and autonomic responses (mean arterial pressure – MAP; heart rate - HR and cutaneous temperature of the tail – CT) evoked by aversive context were measured during test session for 10 min. It was administered 0.1μL of saline (n=7-10), agonist CRF urocortin (n=9), CRF1 antagonist CP376395 (n=5-6) or CRF2 antagonist K41498 (n=5-7) 10 min before test. Compared to control animals, urocortin 0.01nmol significantly increased freezing ($F_{2,25}$=17.7, P<0.001), and autonomic responses (MAP: $F_{1,255}$=88.9, P<0.001 and HR: $F_{1,255}$=65.9, P<0.001) and decreased the CT (F3,495=66.6, P>0.001) after re-exposure to the aversive context when subjected to a low-intensity protocol. These effects were blocked for CP376395 4.5nmol (freezing: $F_{4,30}$=8.2, P<0,001; MAP: $F_{4,450}$=34.2, P<0.001; HR: $F_{4,450}$=8.8, P<0.001 and CT: $F_{4,450}$=20,5 P<0,001) and also for K41498 0.5nmol (freezing: $F_{3,17}$=5.14, P<0.05; MAP: $F_{3,255}$=20.1, P<0.001; HR: $F_{3,255}$=12.9, P<0.001 and CT: $F_{3,255}$=24.3, P<0.001). Neither CP376395 nor K41498 were able to alter the CER in the low-intensity protocol. However, when the animals were subjected to high-intensity protocol, that is, on the physiologic conditions, antagonist CRF1 reduced the CER (freezing: t=7.5, P< 0.001; MAP: $F_{1,165}$=76,8, P< 0,001; HR: $F_{1,165}$=105,6, P< 0,001 and CT: F2,225=20.3 P>0.001), but not K41498 (freezing: t=0.96, P>0.05; MAP: $F_{1,195}$=3.78, P>0.05; HR: $F_{1,195}$=1.73, P>0.05 e CT: $F_{1,195}$=0.63, P>0.05). Our findings support that CRFergic system in the BNST, specifically the CRF1-receptors, are involved in the expression of CFC.

136. **Fear Conditioning in Adult Zebrafish (Danio rerio)**. D. Vira, R. E. Blaser, University of San Diego. Simple parametric variations of trial spacing were used to examine fear conditioning in adult zebrafish. In each of three experiments, zebrafish were exposed to 16 light-shock pairings (Experimental), or unpaired light and shock (Control), followed by four extinction exposures to the light. In the first experiment, animals received four trials each day (Blocked trials). In the second experiment, animals received one trial each day (Spaced trials). In the third experiment, animals received all 16 trials in one day (Massed trials). All animals received the four extinction trials in a single session on the following day. Locomotor activity was recorded throughout the experiments, in order to measure a conditioned hyperactivity response. Acquisition was very poor in the Massed trials group, and best in the Blocked trials group. Although the rate of acquisition was fastest in the Blocked trials group, responding during extinction was strongest in the Spaced trials group. Presentation of stimuli and behavioral recording were fully automated using ViewPoint software, and experimental groups of 14 individuals provided clear conditioned responding within a few days of training. Our results indicate that fear conditioning is a robust and efficient technique for measuring learning in zebrafish.

137. **Study of the expression of GluR1 and GluR2 in hippocampus of rats after injury by NMDA and evaluation of the neuroprotective effect of Parawixina 10.** Helene A. Fachim 1, 2, Adriana Colsera Pereira 1, 2, Melina M. Iyomasa 3, Wagner Ferreira dos Santos 1, 2, Maria Luiza Nunes Mamede Rosa 2, 3. It has been shown the involvement of glutamate, through different receptors, on the excitotoxic mechanisms which result on the neuronal death reported in most neurodegenerative disorders of the CNS. In addition, Parawixina 10 (Pwx 10) has been demonstrated to act as neuroprotective in models of injury regulating the glutamatergic neurotransmission through glutamate transporters. The aims of this work were: i) to study, in a time course (24h, 1, 2 and 4 weeks), the changes on the expression of AMPA receptors in rat hippocampus induced by NMDA intrahippocampal injection, and ii) to study the neuroprotective effect of Pwx 10 in this moldel. Male Wistar rats has been used, submitted to stereotaxic surgery for saline or NMDA microinjection into dorsal hippocampus. Some groups of animals were treated with Pwx 10 from 1h or 24h after NMDA. The behavioral test on Morris water maze (MWM) and the Nissl staining were performed for evaluating the extension and efficacy of the NMDA injury and the neuroprotective effect of the Pwx 10 . The expression of the receptors was analyzed by immunohistochemistry. The expression of GFAP and NeuN on the lesioned area has also been investigated by immunofluorescency. It was observed the impaiment of learning and memory functions in the MWM, and intense loss of neuronal cells and glial proliferation in CA1 that received the NMDA, confirming the efficiency of the injury by the agonist. We observed a time course of distinct changes on the expression of GluR1 and GluR2 subunits of AMPA receptors in hippocampus, which may be related to the complex mechanism triggered in response to NMDA injection resulting in a local injury and on the activation of neuronal plasticity. The treatment with Pwx 10 showed neuroprotective effect, being most pronounced when the toxin was administrated from 1h after NMDA. 1 FFCLRP-USP, 2 INeC, 3 FAMECA-FPA.

138. **Effects of exercise reward on spontaneous and amphetamine-induced appetitive ultrasonic vocalizations in rats.** Heyse N., Álvarez G., Brenes J.C., Schwarting R.K.W. Behavioral Neuroscience, Experimental and Physiological Psychology, Faculty of Psychology, Philipps-University of Marburg, Marburg, Germany. Exercise, such as wheel running, is highly rewarding for rodents, which exercise spontaneously and extensively when having access to a wheel. Regarding its relationships with reward and addiction, it is known that exercise can stimulate the same brain reward pathways that are activated by addictive drugs. Also, extensive exercise reduces the rewarding effects of cocaine and heroin suggesting a cross-tolerance effect between both types of rewards. On the other hand, adult rats emit 50-kHz ultrasonic vocalizations (USV), which are thought to signal positive affective states elicited by natural and non-natural rewards. Thus, the analysis of the USV seems to provide a

unique kind of information regarding the affective state of the rat which might not be obtained by conventional behavioral approaches, motivating the study of USV in several appetitive and rewarding situations. However, the effect of exercise reward on 50-kHz calls in rats has not yet been investigated. To this aim, we performed a study in which experimental rats were trained to run a runway maze to daily access a running wheel during 30 min, whereas sedentary controls had access to a locked wheel. Activity and USV were measured in anticipation, during, and after running exercise for 14 consecutive days. Furthermore, the psychostimulatory drug amphetamine was administered systemically at the end of the training period to investigate the potential cross-tolerance effect between exercise and unconditioned drug effects. Evidence about the effects of exercise reward on appetitive USV and behavioural activity during all testing periods will be provided. These data will be also presented in terms of how individual differences in incentive motivation may predict both, exercise performance and amphetamine responsiveness.

139. **Dopamine depletion in dorsomedial or dorsolateral striatum impairs egocentric Cincinnati water maze performance while sparing allocentric Morris water maze learning**. Williams, M.T.; Braun, A.A.; Amos-Kroohs, R.M.; Udobi, K.C.; Skelton, M.R.; Vorhees, C.V. Division of Neurology, Department of Pediatrics, Cincinnati Children's Research Foundation and University of Cincinnati College of Medicine, Cincinnati, Ohio 45229. Both egocentric route-based learning and spatial learning, as assessed by the Cincinnati water maze (CWM) and Morris water maze (MWM), respectively, are impaired following an 80% dopamine (DA) loss in the neostriatum after 6-hydroxydopamine (6-OHDA) injection in rats. The dorsolateral striatum (DLS) and the dorsomedial striatum (DMS) have been implicated in different navigational learning types, namely the DLS is implicated in egocentric learning while the DMS is implicated in spatial learning. This experiment tested whether selective DA loss through 6-OHDA injection in the DMS or DLS would impair one or both types of navigation. Both DLS and DMS DA loss significantly impaired route-based CWM learning, without affecting spatial or cued MWM performance. DLS 6-OHDA caused 75% DA loss in this region, with no changes in other monoamine levels in the DLS or DMS. DMS 6-OHDA injection caused a 62% DA loss in this region, without affecting other monoamine levels in the DMS or DLS. The results indicate a role for DA in DLS and DMS regions in route-based egocentric but not spatial learning and memory. Spatial learning deficits may require more pervasive monoamine reductions throughout the neostriatum before exhibiting deficits. This is the first study to implicate DLS and DMS DA in route-based navigation.

140. **Cortical motor dominance and movement-related cortical potentials associated with finger force production**. Huai-Hsiao Chiang, Chung-Yuan Christian University, Taiwan. The findings of movement-related cortical potentials associated with motor effectors have shown that multiple movement parameters were controlled by human body, such as timing, force, orientation, and acceleration, etc. However, some constraints subsisted during movement control and execution, such as finger interdependence or finger neuro-anatomical factors. In the past, rate of force development was used to examine the control of finger force production. The mechanism within varied rates of force development during force production associated with higher level of motor system still remained unknown. In terms of motor effectors, the controls of muscles and cortical activations have shown parsimonious adaptation in finger interdependence. The control of force is thought to be changed after specific execution of fingers on both behavioral and cortical level of analyses. This study tried to apply specific feedback to investigate the mechanism of neuro-motor adaptation related to six different rates of force development. 15 college students were required to produce several effector-related tasks associated with force control after motor learning. Force outputs and movement-related cortical potentials were collected and a three-way repeated-measured ANOVA in terms of motor learning, nominal force levels and rates of force development were used for analyses. We found that there were existing different control mechanisms within fingers in terms of different end-effectors. The AVOVA indicated that there were significant effects during after practice for both the nominal force levels and rates of force development. Not surprisingly, larger enslaving effect was found on the finger directly adjacent to the master finger for both force increment and decrement phases. The results and implications of this study would further explore the behavior-brain relationships. It is suggested that the underlying mechanism of finger coordination or the complex motor system could be recognized neurophysiologically and cognitively.

141. **Spatial learning in the plus-maze discriminative avoidance task: Role of proximal and distal cues and CA1 activity**. Leão, A.H.F.F. (1), Medeiros, A.M. (1), Apolinário, G.K.S. (1), Cabral, A. (1), Ribeiro, A.M. (1), Barbosa, F.F. (2); Silva, R.H. (1); (1) Memory Studies Laboratory, Physiology Department, Universidade Federal do Rio Grande do Norte, Natal, Brazil; (2) Memory Studies Laboratory, Psychology Department, Universidade Federal da Paraíba, João Pessoa, Brazil. Previous studies have demonstrated that an adequate performance in the plus-maze discriminative avoidance task (PMDAT, a task used to investigate memory and anxiety interactions in rodents) depends on the activity of the basolateral amygdala and an optimal anxiety level. However, the role of hippocampal-dependent learning in the performance of rats in this task remains to be studied. PMDAT is performed in an elevated plus-maze, with two open and two enclosed arms, one of which presenting aversive stimuli (light and noise) during the training (but not the test) session. Experiment I aimed to assess the role of proximal and distal cues in learning the task. Rats were submitted to a standard training session and tested in the presence (+) or absence (-) of proximal (Prox) and distal (Dist) cues (groups: Prox+/Dist+, Prox+/Dist-, Prox-

/Dist+ and Prox-/Dist-). Analysis of the time in aversive arm versus non-aversive arm revealed that only Prox+/Dist+ and Prox+/Dist- discriminated the aversive arm. Experiment II aimed to assess on the role of the activity in the dorsal hippocampus (subarea CA1) in learning the task. Temporary bilateral inactivation of dorsal CA1 was conducted with muscimol (0.05 µg, 0.1 µg, and 0.2 µg) prior to the training session. Muscimol impaired the performance in a dose dependent manner, increasing aversive arm exploration in the test. In conclusion, proximal cues are more relevant that distal cues for learning the PMDAT. In addition, the results indicate that dorsal hippocampus (CA1) plays a role in learning this task.

142. **Carnivore urine and its component 2-phenylethylamine (PEA) activate the brain fear circuitry and elicit defensive behavior in rats**. Wernecke, K.1,3; Vincenz, D.2,3; Goldschmidt, J.2,3; Fendt, M.1,3 1Institute for Pharmacology and Toxicology, Otto-von-Guericke-University, Magdeburg, Germany; 2Leibniz Institute for Neurobiology, Magdeburg, Germany; 3Center for Behavioral Brain Sciences, Magdeburg, Germany. In response to predator odors, prey animals display a variety of innate defensive behaviors in order to reduce the probability of being attacked. Such anti-predatory responses mainly include escape/avoidance responses, freezing and risk assessment behaviors. Recently, Ferrero and colleagues (2011) identified 2-phenylethylamine (PEA) to be a natural component of carnivore urine that is innately recognized by rodents and triggers fear responses. In contrast to other predator odors discussed in the literature (e.g., cat fur odor, trimethylthiazoline), PEA is not specific for one carnivore species but is found in the urine of all carnivores investigated so far. In the present study, we used carnivore urine (fox, mountain lion, wolf) and PEA as olfactory stimuli to induce defensive behavior in predator-naive laboratory rats in order to investigate the induced defensive behavior and the neural circuitry underlying this fear behavior. We found that during exposure to carnivore urine and different concentrations of PEA, Sprague Dawley rats displayed robust avoidance responses towards the odor sources. These behavioral effects were notably weaker in Wistar rats. Using fox urine, we started to explore the neural substrates that are activated during the expression of carnivore urine and PEA-induced defensive behavior. First preliminary data using in vivo single-photon emission computed tomography (SPECT) imaging of regional cerebral blood flow showed that, among others, the amygdala and the ventral hippocampus are activated by carnivore urine, whereas parts of the prefrontal cortex are inhibited. Currently, the behavioral relevance of these brain sites for predator odor-induced defensive behavior is investigated by means of local muscimol injections.

143. **Sleep and navigation: Does sleep differentially modulate cognitive strategies of navigation?** Naveen Kashyap, IIT Guwahati, India. Humans employ different cognitive strategies for navigating the environment. Two important strategies for such environmental navigation employ either the cognitive map of the environment (spatial memory) or making navigation choices with respect to body motion, independent of landmarks in the environment. Previous research suggests that stage 2 sleep spindles in particular, improves hippocampal dependent spatial learning & memory in humans and non-human primates alike. The improvement during sleep of hippocampal dependent memories is believed to result from improved hippocampal-neocortical interaction in terms of increased sleep spindles. Aim: The present study aims at evaluating the role played by sleep on different cognitive strategies of navigation in a virtual environment. Data: Ten healthy paid participant (mean age: 22.5 yrs, all males) participated in the study. Each participant spent one adaptation night, one experimental night (undisturbed sleep) and second experimental night (sleep deprived) in the sleep laboratory, each night separated from the other by at least one fortnight. In addition on the two experimental nights the subject performed on a virtual navigation task twice, at learning and again at recall using any one strategy. Results: Data was analyzed using 2x2 Between Group (with Repeated Measure on Variable Sleep/Wake) ANOVA with cognitive strategies as Between subject factor and Sleep/Wake as Within Subject factor and time in seconds to complete the navigation task as DV. The F value obtained from the data analysis suggests that there are differences between subject's performance on sleep & wake nights across the cognitive strategies groups and these differences were highly significant ($F_{0.95}(1, 6) = 136.458$, $p<0.01$. However when the performances were compared across the cognitive strategies used by subjects during sleep and wake nights the results obtained were significant at $p=0.1$; ($F_{0.95}(1, 6) = 2.260$, $p>0.05$). Conclusion: In conclusion in the present study we found the sleep benefits spatial memory over no-sleep. Also sleep does differentially modulate cognitive strategies of navigation.

144. **Systematic assessment of learning phenotypes in mutant mouse lines using automated home cage analysis**. Remmelink, E. 1,2,3; Loos, M. 1; Maroteaux, G. 2; Smit, A.B. 3; Verhage, M. 2 1 Sylics (Synaptologics BV), Amsterdam, The Netherlands; 2 Department of Functional Genomics, VU University, Amsterdam, The Netherlands; 3 Department of Molecular and Cellular Neurobiology, VU University, Amsterdam, The Netherlands. The characterization of behavior of genetically modified mice provides a powerful tool in understanding the biological mechanisms underlying neuropsychological disorders. To optimally exploit the expanding number of genetic mouse models of human diseases, and to systematically compare behavioral profiles of these mice, there is a need for efficient behavioral screening systems. This led us to optimize a high-throughput testing protocol for mice requiring no human interference in an automated home cage environment (PhenoTyper) and to develop new data-mining algorithms to better assess the complexity of mouse behavior in the PhenoTyper. The protocol combines observations of spontaneous behavior with two different learning tests: an operant conditioning task, and an avoidance learning paradigm. C57BL/6J mice perform well in both learning paradigms.

Moreover, C57BL/6J mice show few extreme observations and low within-strain variability in spontaneous behavior, which make it an optimal strain for studying genetic manipulations. By systematically analyzing over 40 different genetic mutations on a C57BL/6J genetic background, we were able to identify novel genes involved in learning. In conclusion, this protocol for automated characterization of mice on different aspects of behavior is an efficient initial screening tool to detect learning phenotypes in mutant mouse lines.

145. **Intensity-dependent effects of background noise on motor learning and performance in mice**. Nishijima, T.1; Hosokawa, M.1; Amemiya, S.1,2; Kita, I.1 1 Department of Human Health Schences, Tokyo Metropolitan University, Hachioji, Tokyo JAPAN, 2 Department of Neuroscience, University of Minnesota, Minneapolis, MN USA. Environmental factors, including background noise (BGN), affect learning and performance of various tasks. We have previously demonstrated that BGN at 70 dB intensity improved learning of T-maze task in rats, whereas this improvement was not evident at 100 dB-BGN (Amemiya et al., 2010). The aim of this study was to test a hypothesis that such a so-called inverted U-shaped relationship also exists between level of BGN and motor learning and performance. This hypothesis is well known in a sport science field; however, supporting evidence are still lacking. Male C57BL/6 mice were used for the all experiments. Motor learning and performance were assessed by a rotarod apparatus (ENV-576M, MedAssociate Inc). In the first experiment, we examined effects of BGN (white noise) at different intensities (40 dB control, 70 dB, and 100 dB) on motor learning in an accelerating rotarod task, but we found no significant effects. Next, we examined effects of BGN at different intensities on motor performance. Before a performance test, all the mice underwent rotarod training for 5 consecutive days. Then, the mice were randomly assigned to each of the three groups (40 dB control, 70 dB, and 100 dB) so as to the averaged time on the rod during training period was the same between group. We found a significant extension in the time on the rod in 70 dB compared to control and 100 dB group. In a separate set of experiment, we found that exposure to BGN tended to increase c-Fos immunoreactivity in the nucleus of the hypothalamus, the central amygdala, and the cingulate cortex in an intensity-dependent manner. These results suggest that a moderate intensity of BGN contributes to enhance motor performance but not to improve motor learning, which might be regulated by modest activation of the neural circuitries of stress, emotional, and arousal response.

146. **Role of BDNF/TrkB-signaling in the acquisition and consolidation of fear memories**. Endres T., Institute of Physiology, Otto-von-Guericke University, Magdeburg, Germany Lessmann V., Institute of Physiology, Otto-von-Guericke University, Magdeburg, Germany, Center for Behavioral Brain Sciences (CBBS), Magdeburg, Germany Schulz-Klaus B., Animal Physiology, Institute of Zoology, University of Tübingen, Tübingen, Germany. The neurotrophin BDNF (brain-derived neurotrophic factor) has been shown to be an important mediator of synaptic plasticity and is crucially involved in learning and memory processes. Several recent studies have demonstrated a crucial role of BDNF also in amygdala-dependent cued fear learning. To further pinpoint the time course of BDNF signaling in fear learning, we started to pharmacologically interfere with BDNF/TrkB signaling by application of the Trk-inhibitor K252a into the basolateral amygdala. Here we could identify two distinct time points of BDNF/TrkB-signaling for the acquisition and consolidation of fear memories. Recently it has been shown that, besides in the amygdala, also in the prelimbic medioprefrontal cortex BDNF/TrkB-signaling is crucially involved in the consolidation of cued fear memories (Choi et al., 2010, PNAS). To further elucidate the involvement of BDNF/TrkB signaling in cued fear learning beyond the amygdala, we focused on the perirhinal cortex (PRhC), which has been demonstrated to be also crucially involved in cued fear learning. We first analyzed the levels of BDNF protein in the PRhC at several time points after fear conditioning by using a sensitive BDNF-ELISA. Here we observed a strong increase in BDNF protein 120 min after fear conditioning. We next administered the Trk-inhibitor K252a at this time point locally into the PRhC and thereby observed complete inhibition of the formation of fear memories. In conclusion, these results further stress the important role of BDNF/TrkB-signaling in the acquisition and consolidation of amygdala-dependent fear learning. Furthermore, these results are the first data demonstrating a crucial role for BDNF/TrkB-signaling in the PRhC in the formation of fear memories.

147. **The role of amygdala nuclei in the active vs. reactive threat responding**. *Raquel C. R. Martinez1,2, Nikita Gupta2, Gabriel Lázaro-Muñoz2, Robert Sears2, Caroline Cruz de Oliveira1, Marina Correa de Castro1, Erich Talamoni Fonoff1, Manoel Jacobsen Teixeira1, José Pinhata Otoch1, Joseph E. LeDoux2,3, Christopher K. Cain2,3 1-University of Sao Paulo, LIM 26 - HCFMUSP, Av. Dr. Arnaldo, 455, 4o. andar - Cerqueira Cesar - CEP: 01246-903 - Sao Paulo - SP - Brazil 2-Center for Neuroscience, New York University, 4 Washington Place, New York – New York, 10003, USA 3-Emotional Brain Institute, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York, 10962, USA. Performance of instrumental active avoidance (AA) is constrained by Pavlovian defensive reactions such as freezing. Both AA and freezing depend on the lateral amygdala (LA) for learning and initial performance, however, these opposing behavioral responses to a threatening situation appear to rely on different outputs of the LA. Conditioned freezing critically depends on the central amygdala (CE) whereas AA depends on the basal amygdala. Interestingly, rats that freeze excessively and perform poorly in the AA task show rescued AA performance following CE lesions that abolish conditioned freezing. In these experiments we attempt to identify amygdala nuclei, and subregions within these nuclei, that contribute to the competition between instrumental and Pavlovian responses with AA training. Amygdala

expression of the immediate-early gene c-fos was measured shortly after a shock-free test of Sidman AA performance in rats. c-fos was activated throughout the amygdala compared to box controls, however, poor AA performers showed significantly less activation in most areas examined. Interestingly, only three regions showed significant correlations between behavioral performance and c-fos expression: the dorsal part of LA, the lateral part of CE and the anterior part of the medial amygdala (ME). In each of these areas, c-fos expression correlated positively with AA responding and negatively with freezing. Thus, this unbiased approach suggests that LA, CE and ME may play important roles in the competitive selection of defensive actions vs reactions in threatening situations.

148. **A single social defeat stress provokes short- and long-term anxiogenic-like effects in mice.** 1,2Cipriano, A.C., 2Gomes, K.S., 1,2Nunes-de-Souza, R.L. 1Joint Graduate Program in Physiological Sciences UFSCar/UNESP, 2Lab. Pharmacology, School of Pharmaceutical Sciences, Sao Paulo State University, UNESP, Brazil. The exposure to stressors clearly enhances the vulnerability to neuropsychiatric diseases. As social stress is a chronic or recurring factor for nearly all high animal species, animal models based on social conflicts have been developed. This study investigated the effects of a single exposure to the social defeat stress on the behavior of mice subjected to the elevated plus-maze (EPM) 5 minutes and 10 days after the end of the stress. Adult male Swiss mice (n= 9-12/group) were exposed to a male aggressive resident mouse (social defeat stress Group) or to a non-aggressive mouse (control Group). Five minutes or 10 days later, each mouse was placed on the EPM and the anxiety indices (% open-arm entries and % open-arm time: %OE and %OT) and locomotor activity (closed arm entries: CE) were recorded during a 5-min session. Student's t-test for independent samples revealed a reduction of both %OE and %OT, recorded 5 min ($t(22) = 3.02$, $p < 0.01$) ($t(22) = 2.22$, $p < 0.05$) or 10 days (%OE: $t(17) = 2.90$, $p < 0.02$; %OT: $t(17) = 2.35$, $p < 0.05$) after the social defeat stress when compared to the control group. Social defeat stress mice displayed higher CE than control group, however only when they were exposed to the EPM 10 days after the aggressive confront ($t(17) = -2.46$, $p < 0.05$). Taken together, these results suggest that the social defeat stress can elicit short- and long-term anxiety-like effects in mice exposed to the EPM. Financial support: Fapesp, CNPq, PADC/FCF/UNESP

149. **Increased manganese and iron-deficiency during development in rats affect locomotor responses following pharmacological challenge**. Amos-Kroohs, R., Bloor, C., Guitierrez, A., Hufgard, J., Vorhees, C., Williams, M. Division of Neurology, Cincinnati Children's Research Foundation and Department of Pediatrics, University of Cincinnati. Cincinnati, Ohio, USA. Manganese (Mn), a required trace dietary nutrient, is neurotoxic at higher concentrations. Mn toxicity occurs in children due to factors such as: use of soy baby formulas (naturally high in Mn), well-water exposure, and air pollution in areas with heavy manufacturing. Children have underdeveloped gastrointestinal systems allowing Mn to more readily enter the circulation and accumulate in brain and other tissues. Subclinical iron (Fe) deficiency (FeD; but not anemia) exacerbates Mn toxicity due to bioavailability changes and lack of competitive inhibition. In the United States, FeD affects up to 15% of children under five years old (CDC). To model these effects, pregnant rats and their litters were fed an FeD diet with 90% less Fe than the normal diet or a standard diet from embryonic day 15 through postnatal day (P) 28. Mn treatment consisted of 100 mg/kg Mn (100Mn) given by gavage from P4 to P28 in a subset of animals within each litter. FeD pups treated with Mn are significantly smaller than iron sufficient (FeS) Mn- or VEH-treated controls. Pups were tested for locomotor activity as juveniles and adults. The locomotor testing consisted of 1 h of acclimation, a 1 h response to saline injection, and 2 h response to drug challenge with MK-801 (glutamatergic NMDA antagonist), fenfluramine (FEN, a serotonin releaser), or amphetamine (AMPH, indirect dopamine agonist). FeD animals showed increased responses at P29, but decreased at P60 compared to iron sufficient controls when challenged with AMPH. 100Mn-treated animals, regardless of diet, showed hyperactivity following FEN at P60 but not at P29. Responses after MK-801 showed changes related to diet and Mn treatment. In addition, Mn-treated animals showed decreased anxiety and attenuated responses to positive reinforcement in a sucrose preference test. The data show promise as a model of developmental FeD in combination with elevated Mn.

150. **Hippocampal BDNF mediates the recovery of chronic stress-induced spatial memory deficits in adult male rats.** J. Bryce Ortiz1, Coy M. Mathewson1, Ann N. Hoffman1, Alyssa N. Campbell1, Nickolaus G. Lorson1, Cheryl D. Conrad1. 1Department of Psychology, Arizona State University, Tempe, AZ 85287. Chronic restraint stress-induced deficits in spatial learning and memory can improve following a post-stress recovery period. We investigated brain derived neurotrophic factor (BDNF) as a potential mediator of these chronic stress effects and the recovery process. Adult male Sprague-Dawley rats had their hippocampi bilaterally infused with viral vectors delivering either a siRNA designed against rat BDNF (siRNA) or a scrambled sequence (Scr) and assigned to chronic stress (wire mesh restraint, 6h/d/21d) or non-stressed control (Con) groups. Spatial learning and memory was assessed using an 8-arm, win-stay version of the radial arm water maze (RAWM) either immediately after stressor cessation (Str-Imm) or following a 21-day post-stress recovery period (Str-Rec). The data revealed that while all groups learned the task similarly, differences emerged on the retention trial. Both Str-Imm groups regardless of viral vector contents (Str-Imm-siRNA, Str-Imm-Scr) made statistically more errors in the reference memory domain than did controls. The novel finding was that down-regulating hippocampal BDNF disrupted the recovery of spatial reference memory, as the Str-Rec-siRNA group showed a high number of errors in the RAWM,

and this was statistically similar to rats in the Str-Imm groups. In contrast, the Str-Rec-Scr group improved and showed statistically fewer errors compared to Str-Rec-siRNA, or either Str-Imm group. These data are the first to demonstrate that hippocampal BDNF mediates the recovery from stress-induced hippocampal-dependent spatial memory deficits. We acknowledge the Arizona Biomedical Research Commission and the Arizona State University College of Liberal Arts and Sciences (Conrad) and the NIH IMSD Program via grant number R25GM099650 (Ortiz) and Dr. Ernest Terwilliger for supplying viral vectors for this study.

151. **Regional patterns of neuronal activation associated with nitric oxide synthase inhibitors using c-fos immunohistochemical localisation**. Sherwin, E., 1, 2, Gigliucci, V., 2, 3, Walsh, R., 2, 3, Harkin, A., 2, 3. 1. School of Medicine, Trinity College Dublin, Dublin 2 2. Trinity College Institute of Neuroscience, Trinity College, Dublin 2 3. School of Pharmacy and Pharmaceutical Sciences, Trinity College, Dublin 2. Nitric Oxide Synthase (NOS) inhibitors display antidepressant-like properties in several preclinical behavioural tests. Here, the effects of the nonselective NOS inhibitor Nω-L-nitroarginine (L-NA) and the selective neuronal NOS inhibitor 1-(2-Trifluoromethylphenyl)imidazole (TRIM) were assessed for changes in regional Fos-related immunoreactivity following exposure to the Forced Swimming Test (FST). Male Sprague-Dawley rats (n= 5-6 per group) were treated once daily for three consecutive days with DL-4-p-chlorophenylalanine (pCPA, 150 mg/kg, i.p.), a tryptophan hydroxylase inhibitor, to achieve central serotonin depletion. Animals were then exposed to restraint stress 2 hours per day for three consecutive days and were then subjected to the FST. 24, 5 and 1 hour prior to the test, animals were treated with either L-NA (10mg/kg, i.p.), TRIM (50mg/kg, i.p.) or a saline vehicle (i.p). One hour following the FST, brains were then perfused. Brain regions analyzed included the Prelimbic cortex (PLX), Lateral Septum (LS), Nucleus Accumbens (NAc), Bed Nucleus of the Stria terminalis (BNST), Paraventricular Hypothalamic Nucleus (PVN), Paraventricular Thalamic Nucleus (PVT), Amygdala, and the Dorsal Raphe Nucleus (DRN). A combination of pCPA and restraint stress provoked an increase in immobility time in the FST. The FST increased Fos-related immunoreactivity in all brain regions assessed. But the combination of pCPA and restraint stress failed to influence Fos-related immunoreactivity. Both NOS inhibitors decreased immobility time in keeping with their antidepressant-like properties. Fos-related immmunoreactivity in the PLX and the LS were increased in response to drug treatment. A concomitant reduction in Fos-related immunoreactivity was observed in the NAc, amygdala, and the DRN among others. Differences between L-NA and TRIM were observed in the PVT, PVN and the BNST; where TRIM was found to increase Fos-related immunoreactivity in these regions when compared with L-NA. Moreover, 5-HT depletion and restraint stress diminished TRIM's ability to modulate Fos-related immunoreactivity in several brain regions. In conclusion, NOS inhibitors regulate neuronal activation of cortical and subcortical brain regions in response to the FST, which may correlate with their antidepressant-like properties.

152. **Impaired contextual fear extinction and novel object recognition memory in a chronic psychosocial stress mouse model of brain-gut axis dysfunction**. Kennedy, P.J.1, 2; O'Mahony, C.3; Clarke, G1,2; Dinan, T.G.1,2, Cryan, J.F.1,4 1Alimentary Pharmabiotic Centre; 2Department of Psychiatry; 3Department of Pharmacology and Therapeutics; 4Department of Anatomy and Neuroscience; University College Cork, Cork, Ireland. Chronic psychosocial stress can induce brain-gut axis dysfunction, leading to the onset and exacerbation of symptoms in functional gastrointestinal disorders such as irritable bowel syndrome (IBS). We have established a mouse model based on this premise which produces, in adulthood, a phenotype reminiscent of key aspects of IBS, including visceral hypersensitivity and HPA axis dysfunction. In parallel, emerging clinical research indicates that stress-related hippocampal-mediated cognitive dysfunction may be a core feature of IBS. Translational studies are urgently required to further investigate the molecular and genetic factors underpinning these clinical findings but few studies using pre-clinical models of brain-gut axis dysfunction have focused on cognitive performance. Male C57BL/6J mice were subjected to 19 days chronic unpredictable psychosocial stress (social defeat/overcrowding; SD/OC) followed by behavioral and cognitive assessments; Open field (OF), novel object recognition test (NOR), fear conditioning (FC); Y-maze spatial learning and reversal; Y-maze delayed non-match to sample (DNMS). Body weights were recorded throughout. From day 12-19 of SD/OC stress, stressed animals gained significantly more body weight compared to controls ($p < .001$). During FC stress animals displayed enhanced freezing to context on day 2 (trail 7, $p<0.05$) and day 3 (trail 1, $p< .05$, trial 2, $p=.08$), indicating impaired contextual fear extinction. Stress animals also showed deficits in recognition memory (NOR Discrimination Index, $p< .05$). Stressed and control animals did not differ in anxiety like behavior in the OF or on Y-maze assessments. Our results show that the SD/OC model of brain-gut axis dysfunction also impacts on hippocampal-mediated cognition and further validates the translational relevance of this model. These findings may ultimately enhance our understanding of the underlying pathophysiology of IBS and aid in the development of new pharmacological strategies in the treatment of brain-gut axis disorders.

153. **Social modulation of LiCl-induced "disgust" responses in rats**. Cloutier, C.J., Ossenkopp, K.-P., Kavaliers, M. Department of Psychology and Neuroscience Graduate Program, University of Western Ontario, London, Ontario, Canada. Disgust responses are evident across a range of species and are considered to have their origins in orally based defences against toxicity and pathogens. In rats, disgust is predominately inferred from a distinctive gaping reaction seen when an individual is exposed to a flavoured solution previously paired with an illness inducing toxin. Results of comparative, evolutionary and neurobiological investigations have supported this gaping display

as an indicator of disgust. It has been further shown that, in the absence of illness, exposure to a context previously associated with illness/toxicity elicits anticipatory disgust and gaping. Here we report that social factors can also serve as cues for the display of anticipatory disgust. We show that a social partner previously paired with toxin (LiCl)-induced illness by itself elicits conditioned anticipatory disgust and gaping and ambivalent social avoidance –approach behaviour. In addition, exposure to and interaction with a novel social stimulus can facilitate the propensity for the display of environmental context elicited disgust. These findings show that social factors can both elicit and modulate anticipatory toxin-induced core disgust responses. This support disgust as an adaptive socially modulated toxin avoidance behaviour and provides a further link between core and interpersonal disgust.

154. **Temporary inactivation of the rodent hippocampus: an evaluation of the current methodology**. Tine Gulbrandsen and Rob Sutherland Canadian Centre for Behavioural Neuroscience The University of Lethbridge, Canada. Temporary cellular inactivation is a useful and increasingly popular approach in examining brain function. The method allows for fast-acting manipulations that have the advantage of being reversible. However, there is significant variation in methods across experiments and most authors show very little evidence about the extent or duration of inactivation. Here we investigate the most commonly used method of temporarily inactivating the hippocampus in rats. Immediate early gene activation after electroconvulsive shock was used to determine extent of inactivation using different lengths of infusion needles and one vs. two bilateral infusion sites. Our methods allowed us to uncover some possible confounding factors. We suggest specific variations in the methods which decrease or eliminate these problems. We also investigate the properties of the sodium channel blocker ropivacaine and recommend this drug as a local anesthetic based on its functional profile and established low level of toxicity.

155. **Defensive behavior in an olfactory fear conditioning paradigm: Role of the hippocampus, the periaqueductal gray and the medial hypothalamus**. Carobrez, A.1; Kincheski, G.1; Pavesi, E.2; Kroon, J.1. 1 Depatamento de Farmacologia, Universidade Federal de Santa Catarina, Santa Catarina, Brazil; 2 Department of Anatomy and Neurobiology, University of Tennessee Health Science Center, Tennessee, USA. The olfactory fear conditioning (OFC), where olfactory cues are used as conditioned stimulus (CS), offers controllable measurements for the acquisition and the expression of defensive behavior (DB) associated to traumatic memories. Dangerous olfactory cues such as the predator odor activates neural structures related to DB such as the hypothalamic dorsal premammilary nucleus (PMd), the dorsal periaqueductal gray (PAGd) and the dorsal hippocampus (DH). Based on these facts, in a series of experiments the role of PMd, PAGd and DH during the fear encoding and expression in the OFC paradigm was assessed. Male Wistar rats with implanted cannulas aimed at the PMd, the PAGd or the DH were used. The OFC test was composed of 2 phases, acquisition and expression. The acquisition session was performed in a conditioning chamber, where subjects received infusions of compounds into the PMd, PAGd or DH, in the presence of amylacetate odor (CS). The DB expression sessions occurred in three-day trials in an odor box consisting of 2 compartments (enclosed/open) while the CS source was displayed at the far end of the open compartment. The DB measurements included the time spent in contact to the odor source, or inside the enclosed compartment as well as the time engaged in head out behavior from the enclosed compartment. Results showed that the injection of the beta adrenoceptor agonist isoproterenol in the PMd or of N-methyl-d-aspartate (NMDA) in the PAGd in the presence of the CS were both capable to succeed as an aversive US, promoting CS-US association. On the other hand, the infusion of NMDA into the DH was capable to succeed as a US only when infused after a one foot-shock pairing was previously applied in the presence of the CS. The results reinforce the role for PMd or PAGd as subcortical structures able to interfere with aversive associative learning. In contrast to PAGd or PMd, NMDA stimulation of DH, alone, did not support OFC as a US, but associated with an OFC weak training protocol it strengthened the fear memory consolidation. Financial Support: CAPES; CNPq; FAPESP

156. **Toxin-induced gustatory conditioning in rats: Examining toxin-nutrient trade-offs when ingesting a palatable solution containing small amounts of a toxin.** Good, A.N. 2; Kavaliers, M.1,2; Ossenkopp, K.-P.1,2, 1Department of Psychology and 2Graduate Neuroscience Program, University of Western Ontario, London, Ontario, Canada. Animals foraging for foods which will tend to maximize nutrient, but minimize toxin, ingestion. When an animal ingests a food with a novel flavor and subsequently becomes ill, it will learn to avoid this flavor in the future. In the laboratory, the toxin lithium chloride (LiCl) has been shown to produce such robust conditioned taste avoidances (CTA) in a dose dependent manner. The current study examined changes in drinking behaviors in rats ingesting a sucrose solution varying in caloric content and containing a constant toxin concentration. In an acquisition phase, each sucrose solution contained 0.02 M LiCl and varied in terms of sucrose concentration (0.05 M, 0.10 M, 0.25 M, and 0.50 M). The control sucrose solutions, with the same concentrations, contained 0.02 M sodium chloride (NaCl). In a subsequent extinction phase all rats were presented with sucrose solutions containing only 0.02 M NaCl. Volume intake, number of licks, and microstructural features of licking, including cluster size, were recorded during each session. In the acquisition phase all LiCl groups, except for the 0.50 M sucrose plus LiCl group, displayed significant reductions in fluid intake relative to their respective control groups. Analysis of the cluster size data provided evidence for a toxin-nutrient trade-off for the 0.50 M sucrose plus LiCl group, as these animals exhibited significantly smaller cluster sizes, indicative of reduced palatability,

yet their fluid intake levels were not significantly different from the control group. Such a trade-off was not observed at lower sucrose concentrations.

157. **Female mice heterozygous for creatine transporter deficiency show moderate cognitive deficits.** Hautman, E.R., Kokegne, A.N., Udobi, K.C., Williams, M.T., Vorhees, C.V., Skelton, M.R. Department of Neurology, Cincinnati Children's Research Foundation. Abstract Creatine transporter (CrT) deficiency (CTD) is an X-linked disorder characterized by intellectual disability and a lack of communicative ability. There have been reports that show female carriers are affected by this mutation. We have created CrT knockout (CrT-/y) mice in which males show severe cognitive deficits as a model of this disorder. The purpose of this study was to examine if the female carrier mice show cognitive deficits. Reductions in Cr levels as well as CrT transcript were observed in the brains of the female CrT+/- mice. CrT+/- mice show hyperactivity and increased latency to find the cued platform in the Morris water maze (MWM). CrT+/- female mice showed deficits in MWM hidden platform acquisition but not during reversal testing. Memory deficits on probe trials were observed during both phases. Novel object recognition memory and contextual fear memory were not affected in female CrT+/- mice. Female CrT+/- mice show moderate cognitive deficits, which is consistent with some of the human data. Female CrT+/- mice could prove to be beneficial in further understanding CTD and testing therapeutic approaches.

158. **Correlations between performance in different designs of the stroop task performance and heart rate in young adults**. Amaral, M.E.; Garcia, A.; Carvalho, C.; Tomaz, C. University of Brasilia, DF, Brazil. Stress is an adaptation mechanism to oppose unbalanced homeostasis, associated with autonomic responses such as an increase in heart rate (HR). The present study investigate correlations between performance in different designs of the Stroop task - a mental stress evaluation - and mean heart rate in young adults. The stroop task was performed in three steps: equally congruent and incongruent stimuli (CI), mostly incongruent stimuli (I) and phonetically similar words (PS), categorized in right answer, wrong answer or no-response. Changes in HR were online recorded in 14 subjects (9 Male; age 21.29±1.27). Simultaneously, the performance of the task, was also registered by video and audio. An ANOVA showed no significant difference between the performances in each step. A Pearson's bivariate analysis with performance data and HR in the phonetically similar words step revealed a direct correlation with the amount of no-responses (p=0,046). The HR in the step CI showed the higher mean of all, and it was statistically different than the HR of the steps I (P=0,01) and PS (p=0,03). These results may suggest that the step CI is the most stressful, but since no significant difference was found in the performance between steps we can assume that stress doesn't interfere in the final result of the task performed. The correlation between HR and no-responses in the step PS points to an interference by stress in response inhibition.

159. **Cortical activity and autonomic response during the performance in different conditions of mental**. Carvalho, C.; Garcia, A.; Amaral, M.E.; Tomaz, C. University of Brasilia, DF, Brasília Brazil. Conflict detection and problem resolution is an executive process mediated by the frontal cortex and eliciting response inhibition and interference mechanisms. In the present study we aimed to investigate cortical activities and autonomic responses during performance a mental stress task by demanding responses inhibition. This study evaluated 16 subjects (9 Male; age 21.19±1.22) that performed a Stroop task in three conditions which differ by the level and type of stimulus. First (CON), congruent and incongruent stimuli in the same proportion, second (INC) mostly incongruent and third (SIM) the proportion is the same but words are phonetically similar the color names. Cortical activities during the test were record with electroencephalogram (EEG) simultaneously with a heart rate (HR) monitoring system. Result showed predominant alpha and theta activities in frontal, lateral posterior and mid central areas in all conditions, with significant differences among them. Between the conditions, there was a significant higher beta and gamma activity in right posterior region in CON relative to INC. In alpha band, there was significant higher activation in INC relative to CON in mid posterior region. Between CON and SIM, alpha activity was higher in CON in central and posterior areas, and in beta and alpha there was more activation in posterior areas in CON. Significant HR differences were observed between CON and INC (CON>INC; p=0,01). The results about alpha activity higher in mid central activation suggests the recruitment of response preparation areas, more necessary in INC, when there is more conflict response. Moreover, our results are in agreement with previous studies indicating an association of gamma activity in parietotemporal areas with some excitability evidenced by increase in HR.

160. **Estradiol enhances ingestion in female rats**. Reid, L.D.; Reid, M.L. Rensselaer Polytechnic Institute, Troy, NY, USA. This poster presents characteristic findings concerning the effects of injections of various preparations of estradiol on female rats' ingestion of a variety of ingesta when observed for many days. In addition, we present data associated with females' intake of a mixture of fat and sugar for many days after an injection of estradiol valerate. The initial effects of estradiol are to decrease intakes of ingesta and a transitory loss of bodyweight. The long-term effects, however, are very different: Injections of estradiol valerate increase intakes of palatable alcoholic beverages, saccharin sweetened water, chocolate and white cake mix batter compared to previous levels of intake and to placebo controls. The injections do not increase intakes of ordinary laboratory chow or bitter solutions. Injections of estradiol valerate, as low as 0.19 mg/kg, enhance intakes for days. A dose of 0.38 mg/kg estradiol valerate increased females' intake of fat and sugar for 7 weeks. The increments in intakes are most

apparent if the palatable ingesta are withheld for the initial days when the injections produce transitory weight loss. In addition to estradiol valerate, estradiol benzoate and 17 alpha-ethynylestradiol increase intakes if measurements are taken for many days after injections. The conclusion: the widely held generalization that estradiol decreases intakes is an over generalization, because in some circumstances just the opposite is true.

161. **Prenatal stress predisposes male rats to subordinate status but may facilitate adaptation to stressful social environments**. Scott, K. 1,2; Smeltzer, M. 2; de Kloet, A. 2,3; Flak, J. 2,4; Krause, E. 2,5; Woods, S. 2; Sakai, R. 2 1Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland 2Department of Psychiatry and Behavioral Neurosciences, University of Cincinnati, Cincinnati, OH, USA 3Department of Physiology and Functional Genomics, University of Florida, Gainesville, FL, USA 4Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA 5Department of Pharmacodynamics, University of Florida, Gainesville, FL, USA. Male rats form dominance hierarchies when housed in the Visible Burrow System (VBS), a seminatural model of chronic social stress. Subordinate (SUB) males develop a phenotype that shares many similarities with symptoms of Major Depressive Disorder (MDD). We hypothesized that prenatal stress would predispose adult males to SUB status and exacerbate this phenotype. Pregnant rats exposed to chronic variable stress (CVS) during the last week of gestation had normal weight gain, food intake and litter size, birth weight and sex ratio of pups relative to non-stressed controls. As adults, males were exposed to the VBS or standard housing for 2 wk. Each VBS included one prenatally-stressed (CVS) and one non-prenatally-stressed (NS) male housed with vendor-procured females. Prior to social housing, prenatal treatment had no effect on basal or acute restraint-induced plasma corticosterone of adult males. Prenatally stressed males (CVS) were significantly more likely to become SUB when housed in the VBS ($p<0.01$). However, the SUB phenotype was not enhanced or exacerbated in these males. Following 2 wk of VBS housing, CVS-SUBs had significantly lower plasma corticosterone in comparison with NS-SUBs ($p<0.05$). Furthermore, CVS-SUBs lost less body weight and had better body condition scores than SUBs in traditional VBS studies. These data suggest that while prenatal stress predisposes male rats to SUB status, it does not exacerbate the adverse phenotypic effects typically observed. These findings add further support to the match-mismatch hypothesis, in that prenatal stress is associated with adaptive coping in a socially stressful environment in adulthood. Preliminary data suggest that altered serotonergic development may contribute to these effects.

162. **The effect of (-)-OSU6162 on premature responses in male Lister Hooded rats is dependent on the individual level of emotionality**. Holst, S.1; Alsiö, J.2; Mar, A.2;Fernando, A.2; Goodlett, C.3; Carlsson, A.4; Everitt, B2; Steensland, P.1; Dalley, J.2 1Department of Clinical Neuroscience, Karolinska Institute, Solna, Sweden, 2 Department of Psychology, University of Cambridge , Cambridge, UK, 3 Department of Psychology, Indiana University-Purdue University, Indiana, USA, 4 The Arvid Carlsson Institute for Neuroscience, Institute of Clinical Neuroscience, The Sahlgrenska Academy, Göteborg University, Göteborg, Sweden. (-)-OSU6162 belongs to a new class of compounds which normalize dopaminergic signaling depending on the dopaminergic tone. These compounds inhibit dopaminergic signaling when endogenous dopamine levels are high and enhance the signaling when dopamine levels are low, similar to the action of partial agonists. An unbalanced dopamine tonus is associated with many psychiatric disorders and involved in control of impulsivity. We evaluated the effects of (-)-OSU6162 (0.3, 1, 3 or 10 mg/kg) or vehicle on impulsivity in the five-choice serial reaction time task (5CSRTT) in male Lister Hooded rats. The level of emotionality was estimated in the Novel cage test, which quantifies exploration and risk assessment behaviors as well as locomotor activity. There was no significant effect of (-)-OSU6162 compared to vehicle on the number of premature responses, when looking at the whole group. However, when the rats were divided into two groups based on their level of emotionality the (-)-OSU6162 treatment decreased the number of premature response in the animals with low emotionality, whereas the opposite was found in the animals with high emotionality. Three months after completion of (-)-OSU6162 evaluation the rats were euthanized and their brains dissected. The dopamine receptor D2 and 5-HT-receptor 2A in NAc and mPFC were determined by real-time quantitative RT-PCR (qPCR). It is concluded that (-)-OSU6162 may have potential to improve motor impulsive control, however, the effects are dependent on the animal's level of emotionality.

163. **TRPV1 mRNA expression within the brain of two rat strains differing in nociceptive responsivity**. Manish K. Madasu 1,3; Bright Okine 1, 3; Weredeselam M. Olango 1, 3; Michelle Roche 2, 3; David P. Finn1, 3; 1 Pharmacology and Therapeutics; 2 Physiology, School of Medicine; 3 Galway Neuroscience Centre and Centre for Pain Research, NCBES, National University of Ireland, University Road, Galway, Ireland. The Wistar-Kyoto (WKY) rat is a stress-hyperresponsive strain that exhibits a hyperalgesic phenotype, compared with the Sprague-Dawley (SD) strain[1]. The role of the transient receptor potential vanilloid receptor 1 (TRPV1) in peripheral and central pain processing is well established[2]. The aim of the present study was to complete a comparative analysis of TRPV1 mRNA expression within the brain of WKY and SD rats that had received intra-plantar injection of either saline or formalin. Adult male WKY or SD rats received intra-plantar injection of either saline (SAL) or formalin (FORM) under brief anaesthesia and nociceptive behaviour assessed for 30 minutes to generate composite pain scores (CPS). Rats were killed at the end of the formalin trial period and total RNA was extracted

from frozen punches of periaqueductal grey (PAG), rostroventromedial medulla (RVM), hippocampus (HIPP), amygdala (BLA) and prefrontal cortex (PFC). qRT-PCR was used to determine the expression of mRNA coding for TRPV1. Data were analysed by two-way ANOVA followed by Fisher's LSD post-hoc test. WKY rats exhibited significantly higher formalin-evoked nociceptive behaviour than SD counterparts, indicating a hyperalgesic phenotype. TRPV1 mRNA levels were significantly higher in the dorsal PAG, lower in the lateral PAG and no significant differences in the ventrolateral PAG of saline-treated SD rats compared with WKY counterparts. Formalin treatment was associated with a significant reduction in TRPV1 mRNA expression in the dorsal PAG, which is in contrast to the ventral PAG where there was an increase in mRNA expression in SD rats only. Formalin administration was associated with significant reductions in TRPV1 mRNA expression in the PFC, ventral hippocampus of SD rats only and in the BLA of both WKY and SD rats. These data provide evidence for rapid, dynamic formalin-evoked alterations in TRPV1 gene expression in pain-related brain regions of SD and WKY rats. Acknowledgements: This work was funded by grants from Science Foundation Ireland (10/IN.1/B2976) and College of Science, National University of Ireland, Galway. References: 1. Burke NN, Hayes E, Calpin P, Kerr DM, Moriarty O, Finn DP, Roche M. Enhanced nociceptive responding in two rat models of depression is associated with alterations in monoamine levels in discrete brain regions. Neuroscience. 2010: 1300-13. 2. Szallasi A, Sheta M.Targeting TRPV1 for pain relief: limits, losers and laurels.Expert Opin Investig Drugs. 2012 Sep;21(9):1351-69.

164. **Conjugated equine estrogens impact cognition: Effects replicate in the Sprague-Dawley® rat**. Lauren T. Hewitt1,2, Sarah E. Mennenga1,2, Stephanie V. Koebele1,2, Courtney N. Lavery1,2, Perla K. Mendoza1,2, Heather A. Bimonte-Nelson1,2 1 Department of Psychology, Arizona State University, Tempe, AZ 85287 2 Arizona Alzheimer's Consortium. Aging and menopause are associated with cognitive impairment, which can be obviated by hormone therapy, given optimal parameters. Benefits of 17β-estradiol (E2), the most potent naturally circulating estrogen in women and rats, on cognition have been demonstrated in the rodent literature in multiple rat strains. However, while conjugated equine estrogen (CEE) is the most commonly clinically prescribed hormone therapy, CEE has not been widely tested in rodents for effects on cognition. We have tested the cognitive effects of CEE in the Fischer-344 rat strain, and others have tested effects in the Long-Evans rat strain (e.g., Barha and Galea, 2013). Here, we sought to determine whether the cognitive effects of CEE extend to other rat strains. Thus, we evaluated learning and memory, using the same battery we have utilized previously, in Sprague-Dawley® rats. Subjects received ovariectomy followed by vehicle (sesame oil), E2 (3μg), or CEE (30μg) treatment. Spatial reference and working memory were evaluated using the Water Radial Arm Maze, Morris Water Maze, and Delayed Match-to-Sample tasks. CEE- and E2- treated animals showed enhanced cognitive performance, with greatest enhancements in the working memory domain, replicating our prior effects using Fischer-344 rats. Additional research will assess the dynamics of task-dependent effects and underlying mechanisms, and compare potential effects across strains.

165. **EEG brain mapping of sex differences during performance of tasks requiring inhibitory control mechanisms**. Garcia, A.; Rego, A.; Arcela, A.; Tomaz, C.; Tavares, M.C.H. University of Brasilia, Brasil. The frontal cortex is often related to planning and problem solving, abilities that require behavior output selection and inhibition of probable prepotent responses. Researches indicate enhanced female inhibitory abilities for social and behavioral tasks. But there are still few conclusions on the gender-specific patterns of inhibition for cognitive processes. In this study we aimed to evaluate gender differences in the cortical activity related to inhibitory control. EEG recordings were obtained from 50 volunteers (25 Males; age 21.52±2.32) while performing the Stroop task in three different conditions with different inhibition requirements. First, font colors were the same as designated by the words; second, font colors and the words did not match; and third, the words were phonetically similar to color names but different from those in which they were written. Results showed that alpha and theta band activities were predominant at the frontal, mid-central and left posterior regions with higher activity during the second stage. Women exhibited more cortical activity than men for all bands; except for theta at frontal and occipital left cortex at first stage, when no significant difference was observed. Apart from men, who had no significant difference between conditions in the theta band at the frontal and occipital regions, all the other conditions displayed differences for both genders. The results in posterior areas evidence an association of visual information with the manipulation rule. The activation in central areas emphasizes response preparation and control, demonstrating the need for attention in the performance of incongruent condition. Taken together, our results go in line with the hypothesis of enhanced female inhibitory abilities. –*CNPq*

166. **Age-related differences in performance during an emotional visuo-spatial working memory task: An EEG study**. Belham, Flávia S; Rego, Artur C; Garcia, Ana; Tomaz, Carlos; Tavares, Mª Clotilde H. University of Brasilia, Brasil. Emotional and mnemonic processes share several brain structures, which leads to effects on both ways. The Positivity Effect hypothesis predicts that, while younger adults (YA) focus their attention on negative events, older adults (OA) will remember positive events better. This study aimed at verifying age-related differences on performance and cortical activity during an emotional visuo-spatial working memory task. 27 YA (age=21.4±2.1) and 25 OA (69.6±6.2) performed the Spatial-Delayed Recognition Span Task (identifying the new location of a stimulus presented in a crescent set of identical stimuli) arranged in four conditions: Geometric and

facial (neutral, positive, negative) stimuli, chosen because facial expressions are among the most important emotional displays. YA had more scores than OA ($p<0.001$), but same response time (RT) ($0.150 <0.500$), in all conditions. However, both groups showed a larger RT for geometric than to facial stimuli ($p<0.001$) and to emotional faces than to neutral faces ($p=0.013$), and also greater scores for negative than for positive faces ($p=0.001$). Cortical activation, measured by EEG technique, was concentrated in frontal and middle line regions; but there were differences in Alpha band between the groups with OA showing less evident hemispheric asymmetry and smaller frontal activations ($p<0.05$). Our results do not support the Positivity Effect hypothesis, since both groups showed the same performance pattern. Nevertheless, smaller lateralization and frontal activation in Alpha band seem to be related to aging and reduced performance in OA. -*CNPq*

167. **Influence of exercise on neurotrophin production, cognition, and mood**. Bugatti, M.1 ; Szuhany, K. L.2 ; Otto, M. W.3 123Boston University, MA, USA. Increases in brain-derived neurotrophic factor (BDNF), a protein that promotes neural plasticity, have been associated with improvements in cognitive functioning and mood. A recent meta-analysis identified similar cognitive gains associated with exercise (Smith et al., 2010), with some association between these changes and BDNF activity (Erickson et al., 2012). Research has found strong associations between exercise and upregulation of BDNF, leading to associated mood and cognitive improvements, in rodent populations (Zoladz & Pilc, 2010). However, effects of exercise on BDNF levels in humans are more variable. Given the controversial relationship between exercise and BDNF in humans, the current meta-analysis aimed to identify the overall effect of exercise on BDNF levels as well as identify moderating factors in this relationship. Studies published before February 1, 2013 examining human populations with keywords for exercise and BDNF were included for analysis. Articles were identified through computerized searches conducted in MEDLINE and PsycINFO. Initial searches revealed 62 eligible studies. Current analyses included 21 studies in which data regarding BDNF levels by exercise comparison were reported. Authors plan to contact research groups for remaining data. Preliminary random effects analyses (21 studies, 769 adults) revealed an overall small effect of exercise on BDNF levels ($g = .25$, $p = .04$). Further analysis of change in BDNF from pre-exercise to immediately post-exercise indicated a moderate effect ($n = 12$, $g = .54$, $p < .001$). Additional analyses will examine the effects of moderators, such as exercise regimen, intensity, and frequency, which we hypothesize may impact the effect of exercise on BDNF levels. Results of this meta-analysis indicate a reliable influence of exercise on BDNF, which may be more specific to immediate rather than sustained effects. These results will be discussed within the context of effects of exercise on mood and anxiety disorders as well as cognition.

168. **What social defeat and restraint have in common?** Motta, SC1; Brunton, PJ2; Russell, JA3; Canteras, NS1. 1Dept Anat, Univ. Sao Paulo, Sao Paulo, Brazil; 2Div. of Neurobio., The Roslin Inst. and Royal (Dick) Sch. of Vet. Studies, Univ. of Edinburgh, Edinburgh, United Kingdom; 3Ctr. for Integrative Physiol., Univ. of Edinburgh, Edinburgh, United Kingdom. Two models used in the study of stress are restraint and social defeat. During restraint, stress generation. Although the neural basis for both stress models have been addressed, detailed comparison between them has not been studied and could reveal a dissociation between the neural circuit of entrapment and defeat. The aim of this work was to compare Fos, an indicator of neuronal activation, expression in the hypothalamus of male rats exposed to restraint (10 min) or social defeat (5 min exposure to a dominant conspecific). Results showed a partial overlap in neuronal activation between experimental groups. Restraint triggered intense activation of neurons in the paraventricular nucleus and moderate upregulation of Fos in the anterior part of the anterior nucleus, the juxtadorsomedial region of the lateral hypothalamic area (LHA) and the dorsomedial part of the dorsal premammillary nucleus (PMDdm). While social defeat activated the same areas as restraint, additional Fos expression was observed in the hypothalamic reproductive circuit and the subfornical region of the LHA. Taking into account the afferent information that these hypothalamic sites receive, it is fair to speculate that while the anterior part of the anterior nucleus and the juxtadorsomedial region of the LHA are involved in the entrapment circuit, social defeat may be organized by the reproductive circuit and the subfornical region of the LHA. The PMDdm, in turn, integrates information from both defeat and entrapment circuits, and seems critical to influence the behavioral outcome. Funding: Fapesp # 2010/05905-3.

169. **Contribution of muscarinic cholinergic receptors in the area postrema in conditioned odor aversion**. Gabriel Roldan-Roldan, Dept. of Physiology, Fac. of Medicine, National Autonomous University of Mexico (UNAM), Mexico City. The role of acetylcholine in conditioned odor aversion (COA) was analyzed by evaluating the effect of systemic administration of the non-selective muscarinic antagonists scopolamine and methyl-scopolamine (which does not cross the blood-brain barrier) in different phases of the learning process (acquisition, consolidation, and short and long term memory retrieval). To explore the participation of M1 muscarinic receptors, the selective antagonists biperiden and prienzepine were also tested. Male Wistar rats deprived of water were submitted to a COA protocol during 5 consecutive days. On the third (acquisition) day an orthonasal almond odor was paired with an i.p. injection of LiCl (0.15 M). Results show that scopolamine induced a dose-dependent impairment on acquisition and memory retrieval, but not on memory consolidation or stimuli association. Interestingly, methyl-scopolamine had the same effect but only during acquisition. Biperiden and pirenzepine reproduces the amnesic effects of the non-selective antagonists, but only on acquisition. To explain the

paradoxical effect of peripheral antagonists on COA, we lesioned the area postrema (a key structure for toxicophobic conditioning) with monosodium glutamate s.c., and analyzed its effects behavioral and immunohistochemically. We conclude that central muscarinic receptors (mainly the M1 subtype) at areas lacking blood-brain barrier (i.e., area postrema) may be responsible for the amnesic effect observed during acquisition. Thus, acetylcholine neurotransmission in the olfactory and visceral pathways appears to be involved in different stages of COA.

Saturday, June 29

8:30-10:30 **Symposium: Behavioural neuroscience in Ireland.** Chairs: **Andrew N. Coogan; Stella Vlachou.** *Tara Suite*

8:30 **Psychoneuroimmunology of the circadian clock.** Andrew Coogan, NUI Maynooth. Circadian rhythms are recurring cycles in physiological, behavioural and other parameters that recur with periods of approximately twenty four hours. Such rhythms are generated by an endogenous circadian timekeeping system, with a master circadian clock located to the suprachiasmatic nucleus (SCN) of the hypothalamus and other circadian timekeeping sites distributed throughout the brain and the periphery. Increasing attention is now being paid to how the immune and circadian systems may influence each other, both in terms of circadian regulation of immune function and in how immune status may impact on an animal's circadian behaviour. We have investigated the long-term consequences of sepsis in the mouse following a peripheral treatment with lipopolysaccharide on circadian function once the acute phase of sepsis has resolved. We find that for the most part the circadian system is intact and that most circadian parameters are not altered compared to saline control animals. However, we do find alterations in photic phase-advancing and altered patterns of PER2 expression in the SCN. We find that LPS-induced behavioural alterations are associated with increased microglial marker expression in the SCN and that these effects are attenuated with the NF-kB pathway inhibitor PDTC. We further report that prior sepsis impacts on subsequent responses of the circadian system to low dose LPS. Further, post-septic animals display a number of changes in cognitive and affective parameters. We discuss the implications of these results for understanding circadian-neuroimmune interactions.

9:00 **GABAB1 receptor subunit isoforms modulate susceptibility and resilience to stress-induced changes in behaviour: Implications for gene x environment interactions in depression and anxiety disorders.** Olivia O'Leary, Department of Anatomy & Neuroscience, University College Cork, Ireland. Chronic or severe stress is a risk factor for psychiatric disorders. However, individual responses to stress vary, and some individuals are more susceptible to the negative effects of stress than others. Thus, it is becoming increasingly clear that a complex interplay between genetic factors and stress contributes to the development of psychiatric disorders. Accumulating evidence suggests a role for $GABA_B$ receptors in stress-related psychiatric disorders including depression and anxiety disorders, but their contribution to the development of the negative effects of stress is unknown. $GABA_B$ receptors are heterodimers of $GABA_{B(1)}$ and $GABA_{B(2)}$ subunits. The predominant $GABA_{B(1)}$ receptor isoforms are $GABA_{B(1a)}$ and $GABA_{B(1b)}$ both of which heterodimerize with $GABA_{B(2)}$ to form functional receptors. The aim of the present study was to determine the role of the $GABA_{B(1a)}$ and $GABA_{B(1b)}$ receptor isoforms in susceptibility to the negative effects of chronic stress. The studies revealed that $GABA_{B(1b)}$ knockout mice show increased resilience to the anhedonic and social withdrawal effects of chronic stress in early life (maternal separation) and in adulthood (social defeat), and that hippocampal $GABA_{B(1b)}$ mRNA expression is increased in a genetic mouse model of depression, the Rouen helpless mice. Unlike $GABA_{B(1b)}$ knock-out mice, $GABA_{B(1a)}$ knockout mice did not exhibit this resilience, and in some instances exhibited increased susceptibility to the negative effects of chronic stress. Further studies suggest that hippocampal neurogenesis and neuronal activity in the nucleus accumbens may be key mechanisms underlying this differential resilience to the effects of chronic stress.

9:30 **GABAB receptors in reward processes: The role of GABAB receptor positive modulators in nicotine dependence.** Vlachou, Styliani; Dublin City University, Faculty of Science and Health, School of Nursing and Human Sciences, Glasnevin, Dublin 9, Ireland. γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain and is implicated in the modulation of central reward processes. Acute or chronic administration of γ-aminobutyric acid B (GABAB) receptor agonists or positive allosteric modulators (PAMs) decreases self-administration of various drugs of abuse (e.g., nicotine, cocaine, ethanol and heroin), and inhibits cue-induced reinstatement of nicotine- and cocaine-seeking behavior. GABAB receptor PAMs may be potentially improved therapeutic compounds for the treatment of drug dependence than GABAB receptor agonists due to fewer adverse side-effects. BHF177, a newly synthesized GABAB receptor PAM, decreased both the reinforcing effects of nicotine and the motivation for nicotine without affecting motivation for natural reinforcers, such as food, using the nicotine self-administration fixed-ratio 5 and progressive ratio procedures, respectively. Further, BHF177 dose-dependently blocked cue-induced reinstatement of nicotine seeking, a putative animal model of relapse in humans, with no effect on food seeking, indicating that BHF177 selectively affects drug seeking and not the motivation to seek natural reinforcers. Finally, chronic treatment with BHF177 decreased nicotine self-administration with only small tolerance developed compared to previous observations with a GABAB receptor agonist. These and most recent similar findings from different research groups suggest that BHF177, or other similar GABAB receptor PAMs, could be useful therapeutics for the treatment of nicotine dependence, by assisting both in smoking cessation by decreasing the reinforcing effects of nicotine, as well as in preventing relapse to smoking in humans.

10:00 **Measuring brain activity in freely-moving rats using electroanalytical methods.** Kealy, J. NUI Maynooth. Amperometric sensors for oxygen and glucose allow for real-time recording from the brain in freely-moving animals. These sensors have been previously used to detect activity- and drug-induced changes in metabolism in a number of brain regions. However, less attention has been paid to the hippocampus compared to other areas despite the importance

of the hippocampus in cognition and disease. Carbon paste electrodes for detecting oxygen and glucose oxidase biosensors for detecting glucose were co-implanted into the hippocampus and allowed to record for several days. Stress-induced changes in neural activity significantly alter concentrations of both analytes in the hippocampus. Similarly, a reduction in neural activity via chloral hydrate-induced anaesthesia causes a significant increase in hippocampal oxygen. Treatment with the carbonic anhydrase inhibitor acetazolamide significantly increases hippocampal oxygen and glucose due to the increase in available oxygen from the periphery. Finally, a 20-minute exploration in a plus-maze causes significant changes in both oxygen and glucose that may reflect use of the hippocampus during exposure to a novel spatial context. These findings provide real-time electrochemical data for the hippocampus which has been previously impossible with traditional methods such as microdialysis or ex vivo analysis. As such, these sensors provide a window into hippocampal function which can be used in conjunction with behavioural, electrophysiological and pharmacological interventions to further elucidate the functions and mechanisms of action of the brain in normal and diseased states. This research was made possible by funding provided by Enterprise Ireland (PC/2009/523 and CP/2011/0103), Science Foundation Ireland (12/TIDA/I2308), NUI Maynooth (John and Pat Hume Scholarship) and the Centre of Applied Science for Health which is funded by the Higher Education Authority under the Programme for Research in Third Level Institutions (PRTLI) Cycle 4.

10:30-11:00 **Coffee/Tea Break**. *Tara Suite*

11:00-12:00 **Keynote: Jaap M. Koolhaas, University of Groningen, The Netherlands. The violent rat brain.** *Tara Suite*

The violent rat brain. Jaap M. Koolhaas and Sietse F. de Boer; Dept. of Behavioral Physiology University of Groningen, The Netherlands. Violence can be defined as a form of escalated aggressive behavior that is expressed out of context and out of inhibitory control, and apparently has lost its adaptive function in social communication. Little is known about the social and environmental factors as well as the underlying neurobiological mechanisms involved in the 'vicious' shift of normal adaptive aggression into violence. In this contribution, a recently developed animal model will be presented that is focused on engendering uncontrolled forms of maladaptive aggressive behavior in a strain of originally feral rats. Most animal models of violence are based on a wide variety of laboratory strains of rats. The genetic relationship between these highly domesticated strains and their feral ancestors is virtually unknown. A comparison of the large individual variation in behavior, physiology and neurobiology of this feral rat strain with the Wistar strain shows that important phenotypes have disappeared in the process of domestication. We show that certain constitutionally aggressive individuals gradually develop, over the course of repetitive exposures of victorious social conflicts, escalated, persistent, indiscriminating and injurious forms of offensive aggression. This latter type of pathology is related to a large individual variation in the negative feedback control of the serotonergic system via the 5-HT1a and 5-HT 1b auto-receptors and the serotonin transporter. Moreover, recent studies support the idea that violence is associated with low oxytocin signaling at the level of the medial amygdala. The feral rat model shows the importance to explore the spectrum of outcomes in a genetically and phenotypically highly variable strain that can be used to select the proper phenotype for further studies. Our studies show that the violent rat can be characterized as proactive and impulsive. Conceptually, this behavioral characterization connects to the rapidly developing field of animal personality and its evolutionary and ecological significance.

12:00-1:30 **Break**

1:30-3:30 **Travel award data blitz**. *Tara Suite*

3:30-4:00 **Coffee/Tea Break**. *Tara Suite*

4:00-6:00 **Symposium: Impulsivity, compulsivity, and addiction.** Chairs: **Heather N. Richardson; Trevor W. Robbins**. *Tara Suite*

4:00 **Prefrontal cortex inhibitory control of cocaine craving - implications for relapse prevention.** Serge H. Ahmed.[1,2] [1]Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France ; [2]CNRS, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France. Recent neuroimaging studies have shown that people with cocaine addiction retain some degree of control over drug craving that correlates with neural activity in the lateral prefrontal cortex (PFC). I will present and discuss similar findings in a rat model of inhibitory control of cocaine seeking. In this model, rats actively seeking cocaine were trained to stop this behavior under a discriminative inhibitory conditioning procedure. Rats quickly learned to stop cocaine seeking, even during drug intoxication and after a long history of cocaine self-administration. Inhibitory control of cocaine-seeking was flexible, sufficiently strong to block cocaine-primed reinstatement and selectively depended on neuronal activity within the prelimbic PFC and associated subcortical circuits. The prelimbic PFC is considered the rodent functional homolog of the human lateral PFC. Thus, parallel evidence in both animal models and humans indicate that recruitment of top-down prefrontal inhibitory control of drug seeking is still functional after

prolonged cocaine use. Preclinical investigation of the mechanisms underlying this capacity may contribute to designing new behavioral and/or pharmacological strategies to promote its recruitment for the prevention of relapse in addiction.

4:30 **Molecular mechanisms underlying compulsivity in addiction.** Jonathan Hollander, Sietse Jonkman, Purva Bali and Paul J. Kenny. The Scripps Research Institute - Florida, Jupiter, FL 33458, USA. Cocaine triggers cellular and molecular alterations in brain reward systems, with cocaine addiction commonly viewed as a disorder of neuroplasticity. However, the molecular mechanisms underlying cocaine-induce remodeling of brain reward systems remains unclear. MicroRNAs (miRNAs) are small (~21–23 nucleotides) noncoding RNA transcripts that regulate gene expression at the post-transcriptional level. Here, we show that disruption of miRNA signaling in dopamine D2 receptor-expressing (D2R) medium spiny neurons of the striatum, achieved through cell-specific ablation of Argonaute-2 (AGO2), dramatically attenuates cocaine reward and reinforcement in mice. Using expression profiling, we show that miR-212 is upregulated in the striatum of rats with extended daily access to cocaine, and which demonstrate addiction-like escalation of daily intake. Virus-mediated miR-212 overexpression decreases, whereas antisense oligonucleotide-mediated knockdown of miR-212 increases, cocaine intake in rats with extended but restricted daily access to the drug. We show that miR-212 controls cocaine intake through at least two mechanisms: First, miR-212 represses SPREAD1, resulting in enhanced RAF1 activity and concomitant sensitization of the cAMP signaling cascade in striatum. miR-212-induced increases in striatal cAMP signaling in response to cocaine results in diminished motivation to consume the drug. Second, miR-212 represses expression of methyl CpG binding protein 2 (MeCP2) and thereby decreases striatal levels of brain-derived neurotropic factor (BDNF) and consequently the motivation to consume the drug. These findings reveal miRNAs in striatum, and miR-212 in particular, as novel regulators of cocaine-induced striatal plasticity that regulate the development of compulsive-like patterns of cocaine use.

5:00 **Adolescence, alcohol, and impulsive choice.** C.A. Boettiger Department of Psychology, Biomedical Research Imaging Center, Bowles Center for Alcohol Studies, and Curriculum in Neurobiology, University of North Carolina, Chapel Hill, NC 27599-3270. Disregarding long-term outcomes is characteristic of substance use disorders (SUDs). This tendency can be measured in the lab using “Now/Later” tasks that quantify choices between immediate (“Now”) versus delayed (“Later”) rewards. “Now” bias is an intermediate phenotype of SUDs amenable to biological investigation, and while little is yet known about the neurobiological bases of Now bias in humans, fMRI studies of Now/Later decision-making suggest the importance of frontal regions. Activity in these areas differs based on alcohol use history, suggesting brain mechanisms for poor decisions in alcoholism. In addition to alcohol history, genetic data suggest that variation in frontal dopamine (DA) levels predict both Now bias and underlying brain activity; low frontal DA is associated with Now bias in adults. Adolescent development alters DA signaling, and interacts with genetic indices of frontal DA to predict Now bias, which suggests that manipulation of DA signaling could effectively change Now bias. Indeed, we find that acute reduction of DA signaling in adult males significantly increases Now bias among carriers of a genetic marker of low frontal DA. Our data support the idea that pharmacological interventions can effectively change Now bias, an approach that holds therapeutic promise for treating SUDs, which are currently under-treated. However, our findings caution that genetic and age factors may substantially impact the outcome of pharmacological interventions.

5:30 **The contributions of impulsivity and compulsivity to the development of neuropsychiatric disorders such as addiction.** TW Robbins. Dept. of Psychology and Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge U.K. Impulsivity is the tendency to act prematurely without foresight. Behavioural and neurobiological analysis of this construct, with evidence from both animal and human studies, defines several dissociable forms depending on distinct cortico-striatal substrates. One form of impulsivity depends on the temporal discounting of reward, another on motor or response disinhibition. Impulsivity is commonly associated with addiction to drugs from different pharmacological classes, but its causal role in human addiction is unclear. We characterize in neurobehavioral and neurochemical terms a rodent model of impulsivity based on premature responding in an attentional task. Evidence is surveyed that high impulsivity on this task precedes the escalation subsequently of cocaine self-administration behavior, and also a tendency toward compulsive cocaine-seeking and to relapse. These results indicate that the vulnerability to stimulant addiction may depend on an impulsivity endophenotype. Implications of these findings for the etiology, development, and treatment of drug addiction are considered. We further consider the construct of compulsivity as a tendency to repeat behaviour despite adverse consequences and compare compulsivity in several neuropsychiatric disorders, including obsessive-compulsive-disorder (OCD) and chronic stimulant abuse. We also define some neuroendophenotypes for OCD based on translational studies in experimental animals. The lecture will be concerned with 'behavioural neuroendophenotypes' of relevance to neuropsychiatry. The focus is on impulsivity and compulsivity, their commonalities and differences, and their utility for understanding the aetiology and possible treatment of drug addiction, attention deficit hyperactivity disorder and obsessive-compulsive disorder. The ultimate aim is to identify impairments in specific behavioral processes that can be linked to the aberrant functioning of discrete neural circuitry, for example within the cortico-striatal pathways.

IBNS 2014 - 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 Red Rock Resort, Las Vegas, Nevada, June 10-15, 2014. 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 16, 2013. Details for submission of proposals will be available on the IBNS website.

Save the Dates

Save the Dates

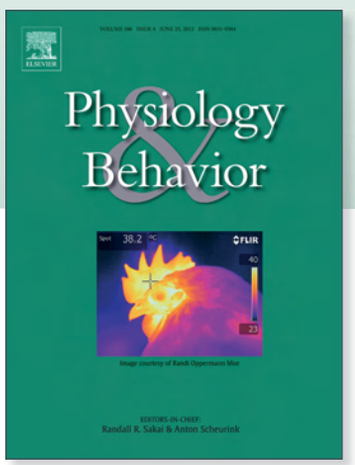
IBNS Annual Conference - June 10-15, 2014
Red Rock Resort, Las Vegas, Nevada

The IBNS 2014 meeting will be held at the Red Rock Resort. This unique and affordable destination captures the energy and excitement of Las Vegas with breathtaking views and offers both business and pleasure while cleverly separating the two into opposite wings of the resort. The off strip location allows the attendees to focus on the content of the meeting, and enjoy the strip just 9 miles away via the complimentary shuttle.

This billion dollar resort is nestled at the gateway of the Red Rock National Conservation area. Each room has views of either the Red Rock Canyons to the west or a sweeping panoramic view of the Las Vegas Strip to the east. The property is conveniently located 14 miles northwest of the Las Vegas McCarran Airport.

Round trip airport transportation is provided to the IBNS group at no charge. The IBNS has negotiated an astonishing $120^{++} room rate for single/double occupancy. See the IBNS website for additional details.

PHYSIOLOGY & BEHAVIOR



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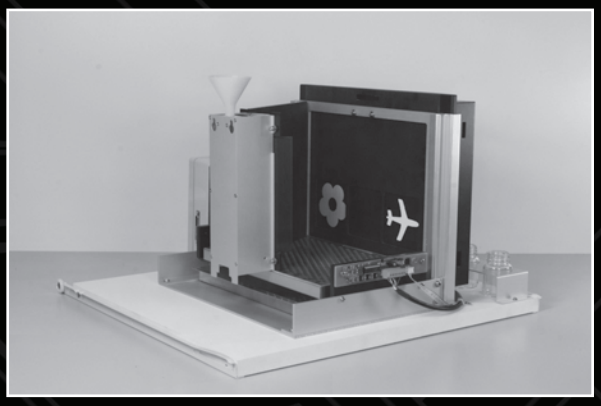

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NOTES:

Summary Program

Tuesday, June 25
10:00-1:00 Council Meeting – *Marconi Room*
2:00-4:00 Student & Post-Doc Only Social – *Matt Ryan Bar.*
4:00-6:00 Registration – *Main Lobby*
7:00-9:00 Welcome Reception – *Guttenberg Suite*

Wednesday, June 26
8:30-10:30 Symposium: Neurobiology & behavioral consequences of estradiol signaling in the brain. Chair: Robert Meisel. *Tara Suite*
8:30-10:30 Symposium: Circadian rhythm and sleep behavior in drosophila. Chair: Norio Ishida. *Guttenberg Suite*
10:30-11:00 Coffee/Tea Break. *Tara Suite*
11:00-12:00 Keynote: John F. Cryan. Mind-altering microbes: role of gut microbiota on brain and behavior. *Tara Suite*
12:00-1:30 Break; Council Meeting (continued) – Coast Restaurant
1:30-3:30 Symposium: Nicotine reinforcement and dependence: Neuroadaptations in stop and go signals. Chair: Nicholas W. Gilpin. *Guttenberg Suite*
1:30-3:30 Symposium: Social aggression. Chair: Newton Sabino Canteras. *Tara Suite*
3:30-4:00 Coffee/Tea Break. *Tara Suite*
4:00-6:00 Symposium: The endocrine disrupting compounds: What they are, where they are and how they change behavior. Chair: Cheryl S. Rosenfeld. *Guttenberg Suite*
4:00-6:00 Symposium: Stop mechanisms in normal behavior and in obsessive compulsive disorder. Chairs: Kurt Hoffman; Henry Szechtman. *Tara Suite*
6:00-8:00 Break
8:00-10:00 Poster Session 1: Animal models of behavioral disorders. *Guttenberg Suite*

Thursday, June 27
8:30-10:30 Symposium: Animal models of autism: Assessing genetic vulnerability, environmental risk factors, and new strategies for intervention. Chair: Tomasz Schneider. *Guttenberg Suite*
8:30-10:30 Symposium: Female vulnerability to depression: From molecules to behavior. Chairs: Debra Bangasser; Christina Dalla. *Tara Suite*
10:30-11:00 Coffee/Tea Break. *Tara Suite*
11:00-12:00 Bench-to-Bedside Lecture: Phil Skolnick. Developing drugs to treat substance use disorders (SUDS): Why haven't we been more successful? *Tara Suite*
12:00-1:30 Break. Workshop: Digital reputation
1:30-3:30 Oral Session 1: TBI, psychosis, and depression. Chair: Stephen Kent. *Tara Suite*
1:30-3:30 Oral Session 2: HIV and addiction. Chair: Mikhail Pletnikov. *Guttenberg Suite*
3:30-4:00 Coffee/Tea Break. *Tara Suite*
4:00-6:00 Symposium: New horizons in nutrition, brain function and behavior. Chair: Robin B. Kanarek. *Guttenberg Suite*
4:00-6:00 Symposium: Broken clocks, inflammatory overload, and social pressures: Modeling stressors of the modern world and their effects on brain and behavior. Chair: Ilia Karatsoreos. *Tara Suite*
6:00-8:00 Break
8:00-10:00 Poster Session 2: Behavioral pharmacology and addiction models. *Guttenberg Suite*

Friday, June 28
8:30-10:30 Symposium: Sex matters: Developmental influences have sex-dependent long-term consequences for behavior. Chair: Susanne Brummelte. *Guttenberg Suite*
8:30-10:30 Symposium: Lost in translation: Improving the predictive validity of animal models for CNS disorders. Chair: David McKinzie. *Tara Suite*
10:30-11:00 Coffee/Tea Break. *Tara Suite*
11:00-12:00 Presidential Lecture: D. Caroline Blanchard. The joy of a good model: Autism, heparan sulfate, and the BTBR mouse. *Tara Suite*
12:00-1:30 Break. Meet The Professionals Lunches.
1:30-3:30 Symposium: Molecular and cellular endophenotypes in neuropsychiatric disease: Homer proteins. Chairs: Karen K. Szumlinski; Tod E. Kippin. *Guttenberg Suite*
1:30-3:30 Symposium: Revisiting the role of medial septal neurons in learning and memory. Chair: Kevin Pang. *Tara Suite*
3:30-4:00 Coffee/Tea Break. *Tara Suite*
4:00-6:00 Symposium: Contribution of early environmental and genetic susceptibility to behaviour related to adult psychopathology. Chairs: Mikhail Pletnikov; John Waddington. *Tara Suite*
4:00-6:00 Symposium: A translational perspective on the neural circuitry of learning and decision making via positive and negative feedback. Chairs: Jonathan Brigman, Jared W. Young. *Guttenberg Suite*
6:00-8:00 Break
8:00-10:00 Poster Session 3: Behavioral biology and development. *Guttenberg Suite*

Saturday, June 29
8:30-10:30 Symposium: Behavioural neuroscience in Ireland. Chairs: Andrew N. Coogan; Stella Vlachou. *Tara Suite*
10:30-11:00 Coffee/Tea Break. *Tara Suite*
11:00-12:00 Keynote: Jaap M. Koolhaas. The violent rat brain. *Tara Suite*
12:00-1:30 Break
1:30-3:30 Travel Award Data Blitz. *Tara Suite*
3:30-4:00 Coffee/Tea Break. *Tara Suite*
4:00-6:00 Symposium: Impulsivity, compulsivity, & addiction. Chairs: Heather N. Richardson; Trevor W. Robbins. *Tara Suite*
6:00-7:00 Business Meeting – Open to all members. *Guttenberg Suite*
8:00-12:00 Awards Banquet. *Tara Suite*