International Behavioral
Neuroscience Society

Annual Meeting
Program and Abstracts

St. Thomas, US Virgin Islands
June 17-21, 2008

Abstracts of the International Behavioral Neuroscience Society, Volume 17, June 2008

TABLE OF CONTENTS

IBNS CENTRAL OFFICE

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Dear Conference Participants, Colleagues, and Friends,

It is my pleasure to welcome you to the 2008 International Behavioral Neuroscience Society Annual Conference! As always, our meeting offers an exciting scientific program that shows how fast our multidisciplinary field is developing. I hope it will fascinate your mind and trigger new ideas, lead to new collaborations and friendships, and give you a glimpse of what other scientists do in our field. In addition to the science, please also don't forget to enjoy this stunningly beautiful tropical paradise!

But also remember, a meeting like this cannot happen without the dedicated hard work of many. Therefore I would like to thank the members of the Program Committee led by Professor Jacki Crawley for putting together such an excellent scientific program, Marianne Van Wagner for meticulously planning and organizing every detail of the meeting, and the Education and Training Committee for selecting the best students for our travel awards and for organizing other student activities. A special thank you goes to Professor John Bruno who played a pivotal role in obtaining and renewing the NIH grant support for our conferences. I would also like to acknowledge the work and dedication of all our Council and Committee members. We appreciate greatly our sponsors who have provided financial support for the meeting: National Institutes of Health, Elsevier Science, Harvard Appartus and Wyeth Research. We also thank NNOXe Pharmaceuticals for funding the Wayner-NNOXe Award. Last but definitely not least, I would like to thank YOU, our conference speakers and poster presenters, for attending our meeting and sharing your work with us!

Welcome to St. Thomas!

Robert Gerlai
President of IBNS

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..... Paul Rushing

We are pleased to announce the recipients of the IBNS Travel Awards for the 2008 meeting in St. Thomas. These awards will be presented at the Awards Banquet on Saturday evening. Award winners will receive a cash award, certificate, and waiver of registration and banquet fees. Congratulations to all.

TRAVEL AWARDS

(listed alphabetically)

Presentations given by the Travel Awardees are indicated in the program by the symbol †.

Mr. Segev Barak, Tel Aviv University, Tel Aviv, ISRAEL

Ms. Corina Bondi, University of Texas Health Science Center at San Antonio, TX, USA

Dr. Evelyn Field, University of Calgary, CANADA

Ms. Katherine Gililland, Oregon Health & Science University, Portland, Oregon, USA

Dr. Jodi Gresack, University of California-San Diego, La Jolla, CA, USA

Mr. Thomas Jarrett, University of North Carolina at Chapel Hill, NC, USA

Mr. Amod Kulkarni, University of Cape Town, SOUTH AFRICA

Ms. Jodi Lukkes, University of South Dakota, Vermillion, SD, USA

Mr. Matthew McMurray, University of North Carolina at Chapel Hill, NC, USA

Mrs. Tori Schaefer, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Dr. Matthew Skelton, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Mr. Markus Wöhr, Philipps-University, Marburg, GERMANY

Dr. Jared Young, University of California-San Diego, La Jolla, CA, USA

Student Travel awardees are presenting orally in the Travel Award Blitz and will also have their research presented in a poster session.

SPONSORS

The IBNS would like to express our gratitude to the following organizations who have given financial support to the 17th International Behavioral Neuroscience Society Conference. This financial support enabled many students to attend the conference and also allowed recruitment of excellent speakers.

National Institute of Mental Health

Grant Number: 2R13MH065244-06

CORPORATE SPONSORS

The IBNS would like to express our gratitude to the following corporate sponsors that are attending the meeting as booth exhibitors and/or have given special financial support to the International Behavioral Neuroscience Society.

Elsevier Science, Inc.
Harvard Apparatus
Wyeth Research

EXHIBITORS

We would also like to thank the following companies that are supporting the IBNS by attending the meeting as booth exhibitors.

Clever Sys., Inc.
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San Diego Instruments
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The Society would like to extend our deep appreciation to the following that are responsible for the success of this meeting:

Program Committee

Jacqueline Crawley (Chair)
Wim Crusio
Andrew Holmes
Christine Hohmann
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Christine Hohmann
Nancy Ostrowski

Local Organizing Committee

Robert Gerlai (Chair)
Robert Adamec
Joe Huston
Wim Crusio
Melanie Paquette

KEYNOTE SPEAKERS

David Amaral, University of California, Davis
Functions of the nonhuman primate amygdala and hippocampus: Evidence from lesion studies in the developing and mature rhesus monkey

Ian Q. Whishaw, University of Lethbridge
S*killed forelimb use in the rat as used to model human neurological conditions*

MATTHEW J. WAYNER-NNOXe PHARMACEUTICALS AWARD

Stephen B. Dunnett, Cardiff University, Wales, UK
Neural transplantation, learning and recovery of function

IBNS FELLOWS SYMPOSIUM

This symposium is in honor of Matthew Wayner's 80th birthday, Founding IBNS President. Both Drs. Eisenstein and Oomura are Founding members of the IBNS and are also Fellows of the Society.

Edward M. Eisenstein

A behavioral homeostasis theory of habituation and sensitization: can it be useful in the early diagnosis of alzheimer's and other cognitive disorders?

Yutaka Oomura

Plastic effect of leptin on the higher brain function.

SPECIAL SYMPOSIA

SENSORY AND PEPTIDERGIC CONTROL OF FOOD HEDONICS: RELATION TO EATING DISORDERS. Sarah Leibowitz (Chair), The Rockefeller University, New York, NY, USA.

STRESS AND ANTI-STRESS SYSTEMS IN THE REGULATION OF ALCOHOL SEEKING. Markus Heilig (Chair), NIAAA, Bethesda, MD, USA.

GLIAL-NEURON INTERACTIONS IN NEUROPSYCHIATRIC AND NEURODEGENERATIVE DISEASES. John P. Bruno (Chair), The Ohio State University, Columbus, OH, USA.

TRANSLATIONAL RESEARCH ON SEXUAL FUNCTIONS: IS IT POSSIBLE? Anders Agmo (Chair), Dept. of Psychology, University of Tromsø, Norway.

NEUROACTIVE STEROIDS IN MENTAL ILLNESSES AND DRUG ABUSE. Giovanni Biggio (Chair), University of Cagliari, Italy.

ANIMAL MODELING OF COGNITION: RELEVANCE TO SCHIZOPHRENIA. Jared Young (Chair), University of California, San Diego, CA, USA.

SATELLITE (Sunday, June 22)

THE NEUROENDOCRINE CONTROL OF ENERGY HOMEOSTASIS. Chairs: Nori Geary and Wolfgang Langhans, Physiology and Behavior Group, Institute of Animal Sciences, ETH Zurich, Schwerzenbach, Switzerland.

Hypothalamic nutrient sensing and its roles in the control of eating and energy balance. **Barry Levin** (*VA Medical Center, East Orange, NJ, USA*)

Amylin, an underappreciated player in the physiological control of eating and energy balance. **Thomas Lutz** (*Institute of Veterinary Physiology, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland*)

Gut peptide-brain crosstalk – What's the role of the vagus. **Wolfgang Langhans** (*Physiology and Behavior Group, Institute of Animal Sciences, ETH Zurich, Schwerzenbach, Switzerland*)

Sex matters – But why? **Nori Geary** (*Physiology and Behavior Group, Institute of Animal Sciences, ETH Zurich, Schwerzenbach, Switzerland*)

Sodium deficiency, salt appetite and mood, - or what every behavioral neuroscientist in the Caribbean should know about the care and feeding of Zombies. **Alan Kim Johnson** (*Psychology Department, University of Iowa, Iowa City, IA, USA*)

Can pharmacotherapy counter the homeostatic mechanisms of the brain. **Alison Strack** (*Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ, USA*)

WORKSHOPS

Student Workshop: Mentoring - from both sides

Organizers: Susan Powell (Education and Training Committee, Chair)
Sarah Johnson (Student Representative to Council)

Having a good mentor as a grad student or post doc can contribute greatly to your choice of career path, as well as your success along that career path. Yet, it is hard to know whether the supervisor you initially choose will turn out to be a great mentor. In this workshop, members of the IBNS Council and Education & Training Committee will talk about their experience as mentees and mentors, with the aim of answering the following questions. What makes a good mentor, and how can you increase your chances of choosing one? Further, what makes a good mentee, and how can you get the most out of your supervisor-student relationship, regardless of the situation?

Panel members Susan Powell, Christine Hohmann, Robert Gerlai and Nancy Ostrowski will then open the discussion to answer questions from attendees. Education & Training Committee members Christine Hohmann and Nancy Ostrowski will also discuss opportunities to forge new mentor-mentee relationships within the behavioral neuroscience community through the IBNS mentoring initiative.

Grant Workshop: Funding Opportunities

Organizer: Christine Hohmann (Program Committee; Education and Training Committee)

A brief overview of various NSF and NIH funding opportunities will be provided during this 30-minute period by Dr. Hohmann. Special emphasis will be placed on funding opportunities for beginning investigators (including training grants) and mechanisms for faculty at predominantly undergraduate and minority serving institutions.

Literature pertaining to these funding opportunities will remain available throughout the meeting at a specially designated table. Dr. Hohmann, Dr. Lambert and other IBNS members experienced with specific grant mechanisms will be standing by to discuss them with interested participants. Appointments for more detailed discussion with these IBNS members can also be made throughout the rest of the conference.

IBNS 2009 - CALL FOR SYMPOSIA and SATELLITE PROPOSALS

The 2009 Annual Meeting of the International Behavioral Neuroscience Society will be held at the Wyndham Grand Bay, Isla Navidad Resort in Manzanillo, Mexico, June 9 – 14, 2009. We look forward to another scientifically excellent conference in a beautiful venue.

The Program Committee is now soliciting proposals for symposia and satellites.

A typical symposium includes four (4) speakers and is scheduled for two (2) hours. The time and date is set by the Program Committee. Satellites are structured and financed by the organizers. Satellite meetings may be held either prior to or after the IBNS meeting dates.

All 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 tentative titles of their talks. Satellites should also include the proposed 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 proposals is September 1, 2008. Please send your proposal by email to the IBNS Central Office, Attn: Marianne Van Wagner, Executive Coordinator, marianne@ibnshomepage.org, with the subject line: Symposia/Satellite Proposal 2009.

PROGRAM NOTES:

- All main events including Lectures, Symposia, Oral Sessions, Business Meeting, Banquet, Poster Sessions, Slide Blitz, Student Workshop and Grant Workshop will be held in the Harbour Ballroom and foyer. The Cocktail Reception will be held on the Sea Cliff Terrace.
- With the exception of the banquet on Saturday evening, no meals are provided.
- Presenting authors are indicated in the program by **bold** type.
- † Indicates Travel Award recipient.

Tuesday, June 17, 2008

8:00 am -12:00 noon	**Council Meeting** - Cellar Room.
1:00 pm -3:00 pm	**Registration** - Harbour Concourse.
4:00 pm - 6:00 pm	**Student Social** – Sea Side Suite (located above CoCo Joes on the beach).
7:00 pm - 9:00 pm	**Registration** - Harbour Concourse. For late arrivals only, the registration desk will be open on Wednesday morning at 7:30 a.m.

Wednesday, June 18, 2008

8:30-9:00 **President's Welcome**. Robert Gerlai

9:00-10:00 **Keynote Lecture, David Amaral,** University of California, Davis. FUNCTIONS OF THE NONHUMAN PRIMATE AMYGDALA AND HIPPOCAMPUS: EVIDENCE FROM LESION STUDIES IN THE DEVELOPING AND MATURE RHESUS MONKEY. Introduction: Jacqueline Crawley

10:00-10:30 **Break & Exhibit Viewing**

10:30-12:30 ***Symposium 1: Stress and anti-stress systems in the regulation of alcohol seeking.*** **Chair: Markus Heilig**

10:30 THE DIFFERENT ROADS TO ROME: POST-DEPENDENT AND GENETICALLY ENCODED RECRUITMENT OF CRH SIGNALING IN EXCESSIVE ALCOHOL INTAKE AND ALCOHOL SEEKING. **Heilig, M.**; Hansson, A.C.; Sommer, W.H.; Thorsell, A.; Cippitelli, A.; Ciccocioppo, R.

11:00 YOHIMBINE, A PHARMACOLOGICAL STRESSOR THAT REINSTATES ALCOHOL-SEEKING AND INDUCES EXCESSIVE ALCOHOL INTAKE IN A CRH DEPENDENT MANNER. **Le, A.D.**

11:30 BLOCKADE OF EXCESSIVE POST-DEPENDENT ALCOHOL INTAKE AND STRESS-INDUCED ALCOHOL SEEKING BY NEUROPEPTIDE Y AND NPY-Y2 ANTAGONISM. **Thorsell, A.**; Cippitelli, A.; Heilig, M.

12:00 NEUROKININ 1 (NK1) RECEPTOR BLOCKADE: A NOVEL ANTI-STRESS BASED MECHANISMS FOR TREATMENT OF ALCOHOLISM. **George, D.T.**; Gilman, J.; Hersh, J.; Thorsell, A.; Gehlert, D.R.; Tauscher, J.T.; Hunt, S.P.; Hommer, D.; Heilig, M.

12:30-2:00 **Break**

2:00-2:30 **Grant Workshop**

2:30-4:30 **Student Workshop**

4:30-5:00 **Break & Exhibit Viewing**

5:00-6:30 ***Oral Session 1: Motivation: Addiction and anxiety.*** **Chairs: Kelly Lambert and Matthew Skelton**

5:00 CONTEXT-INDUCED RELAPSE TO HEROIN SEEKING: NEUROPHARMACOLOGICAL MECHANISMS. **Bossert, J.M.**; Wihbey, K.A.; Koya, E.; Shaham, Y.

5:15 NEURONAL CB2 CANNABINOID RECEPTORS: BEYOND NEUROIMMUNOCANNABINOID ACTIVITY. **Onaivi, E.S.**; Tagliaferro, P.; Brusco, A.; Liu, Q-R.; Akunne, H.; Benno, R.; Akinshola, B.E.; Arinami, T.; Uhl, G.R.; Ishiguro, H.

5:30 CB1 RECEPTORS IN THE DORSOLATERAL PERIAQUEDUCTAL GRAY MODULATE DEFENSIVE RESPONSES IN RATS. **Lisboa, S.**; Resstel, L.; Aguiar, D.; Guimaraes, F.

5:45 EFFECT OF PRENATAL EXPOSURE TO NICOTINE AND THC ON FUTURE REWARD PERCEPTION IN C57BL/6J MICE. **Fetsko, L.A.**

6:00 5-HT2A/2C RECEPTORS EXERT OPPOSING EFFECTS ON LOCOMOTOR ACTIVITY IN MICE. **Powell, S.B.**; Halberstadt, A.L.; van der Heijden, I.; Risbrough, V.B.; Gingrich, J.A.; Geyer, M.A.

6:15 DRUG SAFETY SURVEILLANCE IN CLINICAL TRIALS: THE “NEWER MODEL”. **Ostrowski, N.L.**; Beasely, C. M.

6:30-8:00 **Cocktail Reception** - Sea Cliff Terrace

Thursday, June 19, 2008

8:30-10:30 ***Symposium 2: Neuroactive steroids in mental illnesses and drug abuse.*** **Chair: Giovanni Biggio**

8:30 NEUROACTIVE STEROID-INDUCED MOLECULAR AND BEHAVIOURAL CHANGES DURING SOCIAL ISOLATION STRESS. **Serra, M.**; Biggio, G.

9:00 MANIPULATION OF ALLOPREGNANOLONE LEVELS ALTERS ETHANOL SELF-ADMINISTRATION AND REINSTATEMENT IN MALE C57BL/6 MICE. **Finn, D.A.**; Fretwell, A.M.; Nickel, J.D.; Mark, G.P.; Ford, M.M.

9:30 EFFECTS OF ETHANOL ON GABA-ERGIC NEUROACTIVE STEROIDS IN RATS AND HUMANS MEASURED BY HIGHLY SPECIFIC GC/MS ASSAY. **Morrow, A.L.**; de Wit, H.; O'Buckley, T.K.; Alward, S.E.; Porcu, P.

10:00 NEUROACTIVE STEROIDS IN DEPRESSION, PTSD, AND SCHIZOPHRENIA. **Marx, C.**; Payne, V.; Keefe, R.; Calhoun, P.; Naylor, J.; Kilts, J.; Hamer, R.; Tupler, L.; Beckham, J.; Morey, R.; Connor, K.; Davidson, J.; Shampine, L.

10:30-11:00 **Break & Exhibit Viewing**

11:00-12:00 **Matthew J. Wayner-NNOXe Pharmaceuticals Award Lecture**
Stephen B. Dunnett, Cardiff University, Wales, UK. Neural transplantation, learning and recovery of function. Introduction: Wim Crusio

12:00-4:00 **Break**

4:00-6:00 **Student Travel Award Slide Blitz.** Chairs: Francisco Guimaraes, Victoria Risbrough

MUSCARINIC BLOCKADE IN THE ENTORHINAL CORTEX PREVENTS ACQUISITION OF INATTENTION TO IRRELEVANT STIMULI: RELEVANCE TO SCHIZOPHRENIA. †**Barak, S.**; Weiner, I.

PERFORMANCE ON AN ATTENTIONAL SET-SHIFTING TEST INDUCES FOS EXPRESSION IN RAT PREFRONTAL CORTEX. †**Bondi, C.O.**; Morilak, D.A.

THE EFFECTS OF PRENATAL INFLAMMATION ON THE DEVELOPMENT OF MOTOR AND SOCIAL BEHAVIORS, IN JUVENILE MALE AND FEMALE RATS: IMPLICATIONS FOR THE STUDY OF NEURODEVELOPMENTAL DISORDERS. †**Field, E.F.**; McLeod, S.A.; Pittman, Q.J.

ALLOPREGNANOLONE AND PROGESTERONE LEVELS DURING ETOH WITNDRAWAL IN ADRENALECTOMIZED AND GONADECTOMIZED DBA2/J MALE AND FEMALE MICE. †**Gililland, K.R.**; Tanchuck, M.A.; Finn, D.A.

ROLE OF NOREPINEPHRINE IN CRF-INDUCED DEFICITS IN SENSORIMOTOR GATING. †**Gresack, J.E.**; Wallace, C.; Geyer, M.A.; Risbrough, V.B.

ANIMAL MODELS OF DEPRESSION AND ALCOHOLISM EXHIBIT REDUCED MATERNAL BEHAVIOR. †**Jarrett, T.M.**; Williams, S.K.; Fay, E.E.; McMurray, M.S.; Overstreet, D.H.; Johns, J.M.

INTRANASALLY ADMINISTERED VCP IMPROVES PAIRED-ASSOCIATION LEARNING IN MO/HU APPSWE PS1δE9 MICE IN A NOVEL CHEESE-BOARD MAZE TASK. †**Kulkarni, A.**; Kellaway, L.; Govender, D.; Kotwal, G.

PRE-ADOLESCENT SOCIAL ISOLATION INCREASES FEAR AND ANXIETY BEHAVIOR IN ADULTHOOD. †**Lukkes, J.L.**; Mokin, M.V.; Scholl, J.L.; Forster, G.L.

IN UTERO COCAINE EXPOSURE ALTERS PUP-PRODUCED STIMULI RELEVANT TO MATERNAL CARE. †**McMurray, M.S.**; Jarrett, T.M.; Moy, S.; Styner, M.; Johns, J.M.

COGNITION, ANXIETY, AND DEPRESSIVE-LIKE BEHAVIORS IN PET-1 KNOCK-OUT MICE. †**Schaefer, T.L.**; Vorhees, C.V.; Williams, M.T.

THE ROLE OF ANGIOTENSINOGEN IN BEHAVIORAL DEFICITS INDUCED BY NEONATAL MDMA EXPOSURE. †**Skelton, M.**; Grace, C.; Schaefer, T.; Vorhees, C.; Williams, M.

NEURAL AND PHARMACOLOGICAL CHARACTERIZATION OF SOCIAL APPROACH INDUCED BY PLAYBACK OF 50-KHZ ULTRASONIC VOCALIZATIONS IN THE RAT. †**Wöhr, M.**; Sadananda, M.; Schwarting, R.K.W.

THE RODENT CONTINUOUS PERFORMANCE TEST: IMPACT FOR TRANSLATIONAL DRUG DISCOVERY. †**Young, J.W.**; Geyer, M.A.

6:00-8:30 ***Poster Session 1***

Animal Models of Human Conditions

1. INACTIVATION OF THE RAT MEDIAL PREFRONTAL CORTEX DISRUPTS RISK-BASED DECISION MAKING. **St.Onge, J.R.**; Floresco, S.B.

2. MESOACCUMBENS DOPAMINE MODULATION OF DIFFERENT FORMS OF BEHAVIORAL FLEXIBILITY. **Haluk, D.M.**; Floresco, S.B.

3. DISSOCIABLE EFFECTS OF BLOCKADE OF NR2A AND NR2B NMDA RECEPTORS ON THE ACQUISITION AND EXTINCTION OF CONDITIONED FEAR. **Dalton, G.L.**; Floresco, S.B.; Phillips, A.G.

4. TRANSLATIONAL RESEARCH IN THE STUDY OF SEXUAL SIDE EFFECTS OF ANTIDEPRESSANTS. **Chan, J.S.W.**; Olivier, B.; van Hasselt, F.N.; Snoeren, E.M.S.; Waldinger, M.D.; Oosting, R.S.

5. MEASURING IMPULSIVITY IN MICE. **Granon, S.**; Serreau, P.; Suarez, S.

6. GENERATION AND CHARCTERIZATION OF TPH1, TPH2 AND TPH1/TPH2 DEFICIENT MICE. **Savelieva, K.V.**; Pogorelov, V.M.; Zhao, S.; Rajan, I.; Cullinan, E.; Yang, Q.; Lanthorn, T.H.

7. LOCOMOTION AND COMPULSIVE CHECKING IN THE QUINPIROLE MODEL OF OBSESSIVE-COMPULSIVE DISORDER (OCD). Silva, C.; McMurran, T.; Vega, V.; Graham, D.; Foster, J.; **Szechtman, H.**

8. ROTENONE'S EFFECT ON THE GONADAL FUNCTION ON RATS. **Martínez-Vega, R.**; Valdez-Pinal, O.; Zarraga-Galindo, N.; Rodríguez-Maldonado, E.; Ramírez-Escoto, M.; Rugerio-Vargas, C.; Vergara-Aragón, P.

9. AN INVERTEBRATE MODEL FOR NICOTINE MOTIVATION. **Sellings, L.H.L.**; van der Kooy, D.

10. EFFORT-DRIVEN REWARDS AND LEARNED PERSISTENCE: A NOVEL ANIMAL MODEL FOR BUILDING RESILIENCE AGAINST DEPRESSION. **Hyer, M.**; Crockett, A.; Rzucidlo, A.; Kuehn, J.; Hawley, D.F.; Lambert, K.G.

11. EFFECTS ON A RAT MENOPAUSE MODEL OF AN ALIMENTARY COMPLIMENT BASED ON A BEE PRODUCT. **Zarraga-Galindo, N.**; Meléndez-Rosales, S.; Martínez-Vega, R.; Valdez-Pinal, O.; Palacios-Heredia, M.R.; Rodríguez-Maldonado, E.; Ramírez-Escoto, M.; Rugerio-Vargas, C.; Vergara-Aragón, P.

12. XENON AND NITROUS OXIDE NEUROPROTECTION AGAINST TRANSIENT FOCAL CEREBRAL ISCHEMIA IN RATS: FUNCTIONAL RECOVERY REQUIRES SEVENTY FIVE PERCENT OF IPSILATERAL CORTEX INTEGRITY. **Haelewyn, B.**; Rouillon, C.; Abraini, J.

13. BMY-14802 AS A NOVEL ANTI-DYSKINESIA TREATMENT: SUPPORT FROM A BEHAVIORAL BATTERY IN THE 6-OHDA RAT. **Paquette, M.A.**; Foley, K.E.; Berger, S.P.

14. A DOPAMINE DELIVERY STRATEGY WITH NANOCARRIERS ON A RAT HEMIPARKINSONISM MODEL INDUCED BY 6-OHDA. **Vergara-Aragón, P.**; Martínez-Vega, R.; Valdez-Pinal, O.; Palacios-Heredia, M.R.; Zarraga-Galindo, N.

15. OXIDATIVE STRESS INDUCES NEUROINFLAMMATION AND PROGRESSIVE NEURODEGENERATION IN HIPPOCAMPUS OF RATS EXPOSED TO OZONE. **Rivas-Arancibia, S.**; Guevara-Guzmán, R.; Flores-Rodríguez, T.; López-Vidal, Y.

16. OXIDATIVE-STRESS EFFECTS OVER EXPRESSION OF FOXO3A IN THE INFLAMMATORY RESPONSES IN RAT'S HIPPOCAMPUS EXPOSED TO OZONE. Moreno-Bernal, A.; Sanchez-Vega, R.; Gonzalez-Rivas, D.; Borgonio-Perez,G.; **Rivas-Arancibia, S.**

17. EFFECT OF OXIDATIVE STRESS ON RAT HIPPOCAMPUS CRONICAL EXPOSES TO LOW OZONE DOSES. Rodriguez-Martinez, E.; Sanchez-Vega, R.; Gonzalez-Rivas, S.; Borgonio-Perez, G.; **Rivas-Arancibia, S.**

18. STRIOSOME AND MATRIX PATHOLOGY AND MOTOR DEFICITS IN THE YAC128 MOUSE MODEL OF HUNTINGTON'S DISEASE. **Lawhorn, C.**; Smith, D.M.; Brown, L.L.

19. TIME COURSE FOR MEMANTINE NEUROPROTECTION IN AN NMDA NUCLEUS BASALIS LESION MODEL OF NEURODEGENERATION IN RAT. **Curzon, P.**; Markosyan, S.; Nikkel, A.L.; Salte, K.; Bitner, R.S.; Decker, M.W.

20. OREXIN (HYPOCRETIN) GENE TRANSFER IMPROVES NARCOLEPTIC SYMPTOMS IN OREXIN NULL MICE. Liu, M.; Thankachan, S.; Kaur, S.; Begum, S.; Blanco-Centurion, C.; Sakurai, T.; Yanagisawa, M.; Neve, R.; **Shiromani, P.J.**

21. THE EFFECTS OF PRENATAL INFLAMMATION ON THE DEVELOPMENT OF MOTOR AND SOCIAL BEHAVIORS, IN JUVENILE MALE AND FEMALE RATS: IMPLICATIONS FOR THE STUDY OF NEURODEVELOPMENTAL DISORDERS. †**Field, E.F.**; McLeod, S.A.; Pittman, Q.J.

22. ROLE OF NOREPINEPHRINE IN CRF-INDUCED DEFICITS IN SENSORIMOTOR GATING. †**Gresack, J.E.**; Wallace, C.; Geyer, M.A.; Risbrough, V.B.

23. DEFICITS IN PREPULSE INHIBITION INDUCED BY STIMULATION OF THE LOCUS COERULEUS ARE REVERSED BY BLOCKING NOREPINEPHRINE, BUT NOT DOPAMINE OR SEROTONIN RECEPTORS. **Alsene, K.M.**; Ramaker, M.J.; Schwerin, L.M.; Bakshi, V.P

24. DIFFERENTIAL EFFECTS OF A D1 ANTAGONIST IN SOCIAL BEHAVIOUR AND FEEDING. **Gray, D.G.**; Irwin, J.; Mittelholtz, J.; Choleris, E.

25. COMPREHENSIVE BEHAVIORAL PHENOTYPING OF NEUROLIGIN 3 R451C KNOCKIN MICE. **Chadman, K.K.**; Gong, S.; Scattoni, M.L.; Boltuck, S.; James, J.; Kus, L.; Heintz, N.; Crawley, J.N.

26. FUNCTIONAL $GABA_B$ RECEPTOR CHANGES ASSOCIATED WITH THE MATERNAL *FMR-1* GENOTYPE IN THE MOUSE MODEL OF FRAGILE X SYNDROME. **Zupan, B.**; Toth, M.

27. NEUROBIOLOGICAL CORRELATES OF DEPRESSIVE SYMPTOMOLOGY: AN EXPLORATION OF SEX-DEPENDENT ALTERATIONS IN MOTIVATION, ANHEDONIA, AND COPING STRATEGIES. **Crockett, A.**; Fleming, D.; Tu, K.; Sirkin, M.; Bardi, M.; Kinsley, C.H.; Lambert, K.G.

Human Studies

28. TRAINING-INDUCED FUNCTIONAL ACTIVATION CHANGES IN SCIENTIFIC HYPOTHESIS GENERATION: AN FMRI STUDY. **Kwon, Y.J.**; Choi, Y.H.; Lee, J.K.; Lee, H.N.

29. NEURAL CORRELATES OF CLASSIFICATION ABILITY AS REVEALED BY FMRI OF CLASSIFYING LIVING ORGANISMS. **Lee, I.S.**; Lee, J.K.; Kwon, Y.J.; Yang, I.H.

30. BRAIN-BASED DIFFERENCES BETWEEN CREATING AND UNDERSTANDING CAUSAL KNOWLEDGE. **Lee, J.K.**; Lee, I.S.; Kwon, Y.J.; Kang, M.J.

31. OLFACTORY TESTING FOR EARLY DIAGNOSE OF ALZHEIMER´S DISEASE. **Guevara-Guzman, R.**; Aburto-Arciniega, M.; Severiano, P.

32. REM SLEEP-RELATED MOOD REGULATION IN PATIENTS WITH PARKINSON'S DISEASE. **McNamara, P.**; Auerbach, S.; Harris, E.; Durso, R.

33. ATTENTION, EMOTION AND LANGUAGE IN PATIENTS WITH RIGHT VERSUS LEFT-ONSET PARKINSON'S DISEASE. **McNamara, P.**; Harris, E.; Durso, R.

34. NEUROACTIVE STEROIDS AND SELF-REPORTED PAIN IN VETERANS WHO SERVED DURING OPERATION ENDURING FREEDOM / OPERATION IRAQI FREEDOM. **Kilts, J.D.**; Calnaido, R.P.; Payne, V.M.; Calhoun, P.S.; Tupler, L.A.; Naylor, J.C.; Hamer, R.A.; Morey, R.A.; Beckham, J.C.; Strauss, J.L.; Massing, M.W.; Shampine, L.J.; Connor, K.M.; Davidson, J.R.T.; Marx, C.E.

35. GENDER DIFFERENCES DURING THE PERCEPTION OF SUFFERING EXPERIENCE: A FMRI STUDY. **Barrios, F.A.**; Mercadillo, R.E.; Díaz, J.L.; Salgado, P.M.

36. HUMAN BEHAVIORAL PATTERN MONITOR EXEMPLIFIES DIFFERENCES BETWEEN ACUTE BIPOLAR DISORDER MANIA AND SCHIZOPHRENIA SUBJECTS. **Kincaid, M.J.**; Minassian, A.; Ferguson, E.J.; Young, J.W.; Geyer, M.A.; Paulus, M.P.; Perry, W.

Motivation and Social Behavior

37. ANABOLIC STEROID MODULATION OF NEUROPEPTIDE Y LEVELS IN BRAIN REGIONS CONTROLLING ANXIETY AND REPRODUCTIVE BEHAVIORS IN PUBERTALS RATS. **Santiago-Gascot, M.E.**; Santiago-Castro, S.; Barreto-Estrada, J.L.

38. ANABOLIC STEROIDS AFFECT EMOTIONAL MEMORY IN FEMALE PUBERTAL RATS: POSSIBLE ROLE OF NPY. **Ramos-Pratts, K.**; Santiago-Gascot, M.; Villafane, B.; Pérez-Acevedo, N.; Barreto-Estrada, J.

39. ANABOLIC STEROIDS AFFECT SEXUAL MOTIVATION IN MALE PUBERTAL RAT: POSIBLE ROLE OF NPY. **Parilla-Carrero, J.**; Santiago-Gascot, M.E.; Roig-López, J.L.; Barreto-Estrada, J.L.

40. ANXIETY, SOCIAL, AND SEXUAL BEHAVIOUR AND NEUROENDOCRINE MEASURES IN ADULT RATS PERINATALLY EXPOSED TO CALORIE RESTRICTION. **Kent, S.**; Levay, E.A.; Govic, A.; Hazi, A.; Penman, J.; Paolini, A.G.

41. EFFECTS OF 5-HT1B AND 5-HT 2C RECEPTOR AGONISTS ON BEHAVIORAL SATIETY SEQUENCE IN RATS. **Mancilla-Díaz, J.M.**; López-Alonso, V.E.; Escartín-Pérez, R.E.; Rito-Domingo, M.

42. CENTRAL LEPTIN OR POMC OVEREXPRESSION PARTIALLY RESTORES DECREASED VOLUNTARY WHEEL RUNNING WITH AGE. **Scarpace, P.J.**; Tümer, N.

43. IONIC MECHANISMS OF GHRELIN-INDUCED DEPOLARIZATION ON PEDUNCULOPONTINE TEGMENTAL NEURONS IN RATS: AN IN VITRO STUDY. **Sasaki, K.**; Kim, J.; Nakajima, K.; Wayner, M.J.; Oomura, Y.

44. EFFECTS OF 2E-HEXENAL ON FOOD INTAKE AND ON BRAIN SEROTONIN METABOLISM IN RESTRAINED RATS. **Sasaki, K.**; Mochizuki, T.; Kim, J.; Nakajima, K.; Shimizu, N.; Oomura, Y.

45. STRIATAL CHOLINERGIC CONTROL OF ANTICIPATORY AND CONSUMMATORY FEEDING BEHAVIORS. **Perry, M.L.**; Baldo, B.A.

46. PREFRONTAL CORTEX AND FEEDING: ROLES OF GLUTAMATE AND MONOAMINE SYSTEMS ON FOOD INTAKE AND FEEDING MICROSTRUCTURE. **Mena, J.D.**; Baldo, B.A.

47. SEXUAL PREFERENCE IN MALE RATS PRENATALLY TREATED WITH ATD. **Ferreira-Nuño, A.**; Olayo-Lortia, J.; Fernández-Soto, C.; Reyes-Gordillo, J.; Olivares-Arreola, J.; Velázquez-Moctezuma, J.; Morales-Otal, A.

48. EVALUATION OF PARTNER PREFERENCE IN A 3-CHAMBER TEST BOX USING HORMONE-PRIMED OVARIECTOMIZED LONG EVANS RATS. **Deecher, D.**; Maddage, C.; Bray, J.; Cosmi, S.; Pawlyk, A.; Alfinito, P.

49. ALTERED TRAJECTORIES OF BRAIN AND BEHAVIORAL DEVELOPMENT FOLLOWING NEONATAL SEROTONIN DEPLETION. **Hohmann, C.**; Anderson, M.; Smith-Conner, K.; Blue, M.

50. ENHANCED MATERNAL AGGRESSION IN REPRODUCTIVELY EXPERIENCED DAMS IS ASSOCIATED WITH ALTERATIONS IN CENTRAL VASOPRESSIN AND OXYTOCIN ACTIVITY. Nephew, B.; Bridges, R.S.; **Byrnes, E.M.**

51. EFFECTS OF AN ER-ALPHA AGONIST ON SOCIAL BEHAVIOR IN GONADALLY INTACT AND GONADECTOMIZED MALE AND FEMALE MICE. **Clipperton, A.E.**; Almey, A.; Melichercik, A.; Choleris, E.

52. NEURAL AND PHARMACOLOGICAL CHARACTERIZATION OF SOCIAL APPROACH INDUCED BY PLAYBACK OF 50-KHZ ULTRASONIC VOCALIZATIONS IN THE RAT. †**Wöhr, M.**; Sadananda, M.; Schwarting, R.K.W.

53. EARLY LIFE FAMILY STRUCTURE INFLUENCES EMOTIONALITY AND SPONTANEOUS PARENTAL BEHAVIOR IN ADULT PRAIRIE VOLES. **Ahern, T.H.**; Young, L.J.

Friday, June 20, 2008

8:30-10:30 ***Symposium 3****: Glial-neuron interactions in neuropsychiatric and neurodegenerative diseases.* Chair: John P. Bruno.

8:30 ASTROCYTE-DERIVED KYNURENIC ACID MODULATES ACETYLCHOLINE RELEASE IN PREFRONTAL CORTEX: IMPLICATIONS FOR SCHIZOPHRENIA. **Bruno, J.P.**; Zmarowski, A.; Pellicciari, R.; Schwarcz, R.

9:00 UNUSUAL BACKGROUND GENES IN THE BTBR T+tf/J MOUSE MODEL OF AUTISM INCLUDE A KYNURENIC ACID METABOLIC ENZYME. **Crawley, J.N.**

9:30 OLIGODENDROGLIAL AND MYELIN DEFICITS IN SCHIZOPHRENIA: IMPLICATIONS FOR SALTATORY SIGNAL CONDUCTION AND THE DISCONNECTIVITY SYNDROME. **Haroutunian, V.**; Dracheva, S.; Katsel, P.; Davis, K.L.

10:00 NEURON-GLIA INTERCOMMUNICATION DURING NEUROINFLAMMATION ASSOCIATED WITH ALZHEIMER'S DISEASE AND OTHER NEURO-DEGENERATIVE DISORDERS. **Wenk, G.L.**; Brothers, H.M.; Cerbai, F.; Marchalant, Y.

10:30-11:00 **Break & Exhibit Viewing**

11:00-12:15 ***Oral Session 2:*** *Learning, Memory and Motor Systems.* Chairs: Stefan Brudzynski and Evelyn Field

11:00 NSAID TREATMENT CAN REVERSE INFLAMMATION-INDUCED DEFICITS IN ADULT NEUROGENESIS AND MEMORY. **Ormerod, B.K.**; Lee, S.W.; Palmer, T.D.

11:15 MAGNETIC RESONANCE IMAGING (MRI) OF THE DEVELOPING HUMAN BRAIN: HAND USE AND SEXUAL DIMORPHISMS. **Almli, C.R.**

11:30 ELECTRICAL STIMULATION OF THE POSTERIOR HYPOTHALAMIC NUCLEUS AMELIORATES 6-OHDA INDUCED AKINESIA. **Young, C.K.**; Koke, S.J.; Kiss, Z.H.; Bland, B.H.

11:45 MOTOR-SKILL LEARNING IN A NOVEL RUNNING-WHEEL TASK: CRITICAL ROLE FOR D1 DOPAMINE RECEPTORS IN THE STRIATUM. **Steiner, H.**; Willuhn, I.

12:15-4:00 **Break**

4:00-6:00 ***Symposium 4****: Animal modeling of cognition: Relevance to schizophrenia.* Chair: Jared W. Young.

4:00 FINDING AND DEVELOPING COGNITION ENHANCERS FOR SCHIZOPHRENIA: IS THERE A NEEDLE IN THE HAYSTACK? **Sarter, M.**

4:30 CORTICO-THALAMIC-STRIATAL CIRCUITS UNDERLYING BEHAVIORAL FLEXIBILITY. **Floresco, S.B.**

5:00 COGNITIVE CORRELATES TO PREPULSE INHIBITION IN MAN: APPLICABLE FOR RESEARCH IN RODENTS? **Risbrough, V.B.**

5:30 THE RODENT CONTINUOUS PERFORMANCE TEST: IMPACT FOR TRANSLATIONAL DRUG DISCOVERY. †**Young, J.W.**; Geyer, M.A.

6:00-8:30 ***Poster Session 2***

Learning and Memory

54. EXPLICIT DISASSOCIATION OF A CONDITIONED STIMULUS AND UNCONDITIONED STIMULUS DURING EXTINCTION TRAINING REDUCES BOTH TIME TO ASYMPTOTIC EXTINCTION AND SPONTANEOUS RECOVERY OF A CONDI. **Mickley, G.A.**; DiSorbo, A.; Wilson, G.N.; Huffman, J.; Bacik, S.; Hoxha, Z.; Biada, J.M.; Kim, Y.-H.

55. MUSCARINIC BLOCKADE IN THE ENTORHINAL CORTEX PREVENTS ACQUISITION OF INATTENTION TO IRRELEVANT STIMULI: RELEVANCE TO SCHIZOPHRENIA. †**Barak, S.**; Weiner, I.

56. INTRANASALLY ADMINISTERED VCP IMPROVES PAIRED-ASSOCIATION LEARNING IN MO/HU APPSWE PS1δE9 MICE IN A NOVEL CHEESE-BOARD MAZE TASK. †**Kulkarni, A.**; Kellaway, L.; Govender, D.; Kotwal, G.

57. CRANIAL IRRADIATION IMPAIRS NEUROGENESIS AND COGNITION DISTINCTIVELY IN JUVENILE AND ADULT MICE. **Lee, S.W.**; Palmer, T.D.

58. FUNCTION OF THE CHOLINERGIC AND BETA-ADRENERGIC SYSTEMS DURING ACQUISITION, CONSOLIDATION AND RETRIEVAL OF LONG TERM MEMORY OF ODOURS WITH DIFFERENT EMOTIONAL CONTENT. **Miranda, M.I.**; García, D.; Ortiz-Godina, F.

59. SEX STEROID HORMONE ESTROGEN AND WORKING MEMORY FOR EMOTIONAL FACIAL EXPRESSIONS. Gasbarri, A.; Pompili, A.; d'Onofrio, A.; Cifariello, A.; Falconieri, D.; Tavares, M.C.; Tomaz, C.

60. 5-HT7 ANTAGONIST SB-269970 AND ITS ROLE IN THE MODULATION OF WORKING AND REFERENCE MEMORY IN RATS. Gasbarri, A.; Cifariello, A.; Pompili, A.; **Arnone, B.**; Meneses, A.

61. EMOTIONAL FACIAL EXPRESSIONS IN CAPUCHIN MONKEY (CEBUS APELLA). Tavares, M.C.; d'Onofrio, A.; Marchetti, A.; Abreu, C.T.; Gasbarri, A.; Tomaz, C.

62. HIPPOCAMPAL NR2B-CONTAINING NMDA RECEPTORS ARE ESSENTIAL FOR SPATIAL MEMORY ENCODING. **Brigman, J.L.**; Delpire, E.; Holmes, A.

63. RAPID EFFECTS OF ESTROGEN RECEPTOR ALPHA AND BETA AGONISTS ON LEARNING AND MEMORY. **Phan, A.**; Lancaster, K.E.; MacLusky, N.J.; Choleris, E.

64. PERFORMANCE ON AN ATTENTIONAL SET-SHIFTING TEST INDUCES FOS EXPRESSION IN RAT PREFRONTAL CORTEX. †**Bondi, C.O.**; Morilak, D.A.

Reward and Addiction

65. ADOLESCENT SOCIAL DEFEAT ALTERS RESPONSES TO NOVELTY AND AMPHETAMINE IN ADULT RATS. **Burke, A.R.**; Watt, M.J.; Renner, K.J.; Forster, G.L.

66. EFFECT OF PERIADOLESCENT EXPOSURE TO NICOTINE ON ADULT RAT RESPONSE TO DIAZEPAM IN AN ELEVATED PLUS-MAZE. Anumudu, E.H.; Williams, H.L.; **McMillen, B.A.**

67. INVOLVEMENT OF NUCLEUS ACCUMBENS DOPAMINE IN FAT OVEREATING IN RATS. **Narikiyo, K.**; Shiota, N.; Aou, S.

68. STIMULATION OF DORSAL STRIATAL D2 RECEPTORS ATTENUATES THE KAPPA-OPIOID-MEDIATED LOCOMOTION OF PREWEANLING RATS. **Charntikov, S.**; Herbert, M.S.; Halladay, L.R.; Marquez, E.M.; **McDougall, S.A.**

69. INVOLVEMENT OF THE ORBITOFRONTAL CORTEX IN CONTEXT-INDUCED AND COCAINE-PRIMED REINSTATEMENT OF COCAINE-SEEKING BEHAVIOR IN RATS. **Lasseter, H.C.**; Traina, S.A.; Fuchs, R.A.

70. INVOLVEMENT OF LIMBIC BASAL GANGLIA IN ALCOHOL WITHDRAWAL. **Buck, K.**; Chen, G.

71. CANNABINOID MODULATION OF HAMSTER CIRCADIAN ACTIVITY RHYTHMS. **Gannon, R.**; Sanford, A.M.; Castillo, E.

72. EFFECTS OF REWARDING AND NON-REWARDING DRUGS ON SOCIAL REWARD CONDITIONED PLACE PREFERENCE. **Thiel, K.J.**; Dickey, E.D.; Okun, A.; Routt, V.; Neisewander, J.L.

73. INTRANIGRAL ADMINISTRATION OF A MODULATOR OF ENDOCANNABINOID FUNCTION (AM404) MODIFIES KAINIC ACID-INDUCED MOTOR SEIZURES. Mejía-Toiber, J.; García-Martínez, C.; Romero-Cano, D.; Mendoza M.S.; **Giordano, M.**

74. BEHAVIORAL EFFECTS OF METHAMPHETAMINE TOXICITY ARE TIME AND MOUSE STRAIN SPECIFIC. Phillips, C.; Rhoades, R.; Hodges, A.; Krasnova, I; Cadet, J.; **Hohmann, C.**

75. CHANGE IN SENSITIVITY TO INTRA-HIPPOCAMPAL MICROINJECTION OF FINASTERIDE VS ALLOPREGNANOLONE ON SEIZURE SUSCEPTIBILTY DURING ALCOHOL WITHDRAWAL. **Tanchuck, M.A.**; Gililland, K.R.; Snelling, C.; Mark, G.P.; Finn, D.A.

76. VOCAL AND LOCOMOTOR RESPONSES TO AMPHETAMINE IN THE INBRED LONG-EVANS RATS. **Brudzynski, S.M.**; Duffus, S.; Gibson, B.; Burgdorf, J.

77. STIMULATION OF 5-HT1B RECEPTORS ENHANCES COCAINE REINFORCEMENT YET REDUCES COCAINE-SEEKING BEHAVIOR. **Pentkowski, N.S.**; Browning, J.; Acosta, J.I.; Hamilton, L.; Duke, F.; Neisewander, J.L.

78. INTERACTIVE EFFECTS OF GENE KNOCKOUT OF THE SEROTONIN 1A AND 1B RECEPTORS WITH GENE KNOCKOUT OF THE DOPAMINE TRANSPORTER. **Hall, F.S.**; Perona, M.T.G.; Sora, I.; Tecott, L.H.; Hen, R.; Uhl, G.R.

79. ALLOPREGNANOLONE AND PROGESTERONE LEVELS DURING ETOH WITNDRAWAL IN ADRENALECTOMIZED AND GONADECTOMIZED DBA2/J MALE AND FEMALE MICE. †**Gililland, K.R.**; Tanchuck, M.A.; Finn, D.A.

80. EFFECT OF SYSTEMIC AND INTRA-TEGMENTAL METHAMPHETAMINE ON ACETYLCHOLINE AND DOPAMINE LEVELS IN THE VENTRAL TEGMENTAL AREA IN THE MOUSE. **Dobbs, L.**; Mark, G.P.

81. NEURAL CIRCUITRY OF MEMORY RECONSOLIDATION PROCESSES THAT FACILITATE CONTEXT-INDUCED COCAINE SEEKING. **Ramirez, D.R.**; Xie, X.; Bell, G.H.; Eaddy, J.L.; Fuchs, R.A.

82. ARGON PREVENTS AMPHETAMINE SENSITIZATION. **David, H.N.**; Dhilly, M.; Poisnel, G.; Debruyne, D.; Abraini, J.H.

83. PREFRONTAL AND AMYGDALOID CONTROL OF THE EXPRESSION OF BEHAVIOURAL SENSITIZATION TO AMPHETAMINE. **Degoulet, M.**; Rouillon, C.; David, H.N.; Rostain, J.C.; Abraini, J.H.

84. SUBTYPE-SPECIFIC CHARACTERIZATION OF THE EFFECTS OF POST-RETRIEVAL ß-ADRENOCEPTOR ANTAGONISM IN A COCAINE CONDITIONED PLACE PREFERENCE PARADIGM. **Bernardi, R.E.**; Lattal, K.M.; Berger, S.P.

85. ALCOHOL AFFECTS PHARMACOKINETICS AND PHARMACODYNAMICS OF MDMA. **Jones, B.C.**; Ben-Hamida, S.; Pereira de Vasconcelos, A.; Jackisch, R., Cassel, J.C.

86. CHRONIC PHYSICAL ACTIVITY IN RODENTS INCREASES MU OPIOID RECEPTOR BINDING. **Lawrence, R.C.**; Junor, L.; Ford, K.A.; Wilson, M.A.

87. EFFECTS OF DECREASING AMYGDALAR MU OPIOID RECEPTORS ON ANXIETY RESPONSES. Wilson, M.A.; Ford, K.A.; Smith, L.A.; Zhang, J.; Wilson, S.P.

88. PRENATAL EXPOSURE TO ALCOHOL/NICOTINE ALTERS OXYTOCIN RECEPTOR BINDING BUT NOT mRNA IN ADULT RATS. **Cox, E.T.**; Williams, S.K.; McMurray, M.S.; Jarrett, T.M.; Fay, E.E.; Overstreet, D.H.; Johns, J.M.

89. PRENATAL EXPOSURE TO ALCOHOL/NICOTINE AFFECTS ALCOHOL CONSUMPTION IN ADULT BUT NOT ADOLESCENT RATS. **Williams, S.K.**; McMurray, M.; Jarrett, T.M.; Cox, E.T.; Fay, E.E.; Overstreet, D.H.; Johns, J.M.

90. IN UTERO COCAINE EXPOSURE ALTERS PUP-PRODUCED STIMULI RELEVANT TO MATERNAL CARE. †**McMurray, M.S.**; Jarrett, T.M.; Moy, S.; Styner, M.; Johns, J.M.

91. ANIMAL MODELS OF DEPRESSION AND ALCOHOLISM EXHIBIT REDUCED MATERNAL BEHAVIOR. †**Jarrett, T.M.**; Williams, S.K.; Fay, E.E.; McMurray, M.S.; Overstreet, D.H.; Johns, J.M.

Stress, Anxiety, Fear and Defense

92. ADRENAL ACTIVATION RELATED TO THE WILD RUNNING BEHAVIOR IN THE RAT. Costa, M.M.; Pereira, P.C.; Hage, M.P.; Molico, E.; Miranda, T.; **de Paula, H.M.G.**

93. DIFFERENCES IN OPEN-FIELD AND ELEVATED PLUS-MAZE BEHAVIOR BETWEEN WILD RUNNING-SENSITIVE AND WILD RUNNING-RESISTANT RATS. Pereira, P.C.; Hage, M.P.; Molico, E.; Costa, M.M.; Miranda, T.; **de Paula, H.M.G.**

94. SOCIAL BUFFERING MITIGATES CONDITIONED FEAR RESPONSES WITHOUT PHYSICAL CONTACT IN MALE RATS. **Kiyokawa, Y.**; Takeuchi, Y.; Nishihara, M.; Mori, Y.

95. PERINATAL DIETARY PHYTOESTROGEN EXPOSURE ALTERS USV EXPRESSION DEPENDENT ON AGE ENVIRONMENTAL TEMPERATURE AND GENDER. **Becker, L.A.**; Parker, K.L.; Stewart, P.A.; Lawler, B.; Burns, L.N.; Yeager, J.R.

96. PARENTAL SEROTONIN 1A RECEPTOR GENOTYPE CONTRIBUTES TO ANXIETY-RELATED BEHAVIOR. **Gleason, G.**; Bruening, S.; Toth, M.

97. PRE-ADOLESCENT SOCIAL ISOLATION INCREASES FEAR AND ANXIETY BEHAVIOR IN ADULTHOOD. †**Lukkes, J.L.**; Mokin, M.V.; Scholl, J.L.; Forster, G.L.

98. INFUSION OF GROUP I METABOTROPIC GLUTAMATE RECEPTOR AGONIST WITHIN THE BASOLATERAL COMPLEX PRODUCES ANXIOLYTIC-LIKE EFFECTS IN ESTROGEN-TREATED FEMALE RATS. **De Jesús-Burgos, M.I.**; Ballista-Hernandez, J.; Quiñones-Laracuente, K.; Pérez-Acevedo, N.L.

99. CHRONIC CAFFEINE AND STRESS HAVE A SEX-SPECIFIC EFFECT ON ANXIETY IN RATS. **Pettenuzzo, L.F.**; Noschang, C.; Crema, L.M.; Toigo, E.V.P.; Vendite, D.; Dalmaz, C.

100. ACTIVATION OF VANILLOID-1 (TRPV1) RECEPTORS IN THE DORSOLATERAL PERIAQUEDUTAL GRAY ATTENUATES THE ANXIOLYTIC EFFECTS OF CANNABIDIOL. Campos, A.C.; Terzian, A.L.; Aguiar, D.C.; Moreira, F.A.; **Guimarães, F.S.**

101. NITRIC OXIDE SYNTHASE INHIBITOR INJECTED INTO THE DORSOLATERAL PERIAQUEDUCTAL GREY DECREASES CELLULAR AND BEHAVIORAL CONSEQUENCES OF PREDATOR EXPOSURE IN RATS. **Aguiar, D.C.**; Guimaraes, F.S.

102. ADULT HPA AXIS RESPONSIVITY TO FORCED SWIM OR ISOLATION FOLLOWING NEONATAL EXPOSURE OF RATS TO (+)-METHAMPHETAMINE. **Grace, C.E.**; Williams, M.T.; Vorhees, C.V.

103. A COMPARISON OF THE ELEVATED PLUS AND ELEVATED ZERO MAZE WITH OR WITHOUT DIAZEPAM IN RATS. **Braun, A.A.**; Skelton, M.R.; Vorhees, C.V.; Williams, M.T.

104. THE ROLE OF ANGIOTENSINOGEN IN BEHAVIORAL DEFICITS INDUCED BY NEONATAL MDMA EXPOSURE. †**Skelton, M.**; Grace, C.; Schaefer, T.; Vorhees, C.; Williams, M.

105. COGNITION, ANXIETY, AND DEPRESSIVE-LIKE BEHAVIORS IN PET-1 KNOCK-OUT MICE. †**Schaefer, T.L.**; Vorhees, C.V.; Williams, M.T.

106. MAPPING OF THE OCTOPAMINERGIC SYSTEM IN THE CNS OF THE FRESHWATER PRAWN IN THE CONTEXT OF AGONISTIC BEHAVIOR. **Reyes-Colón, D.**; Vázquez-Acevedo, N.; Rivera-Chéverez, N.M.; Sosa-Lloréns, M.A.

107. HOUSING CONDITIONS BUT NOT PB2+ DURING THE NEONATAL PERIOD IN RATS INTERACTS WITH AN ACUTE STRESSOR ON CORTICOSTERONE RELEASE. **Graham, D.L.**; Grace, C.E.; Schaefer, T.L.; Skelton, M.R.; Vorhees, C.V.; Williams, M.T.

108. INFLUENCE OF RESTRAINT STRESS ON SEROTONERGIC AND NORADRENERGIC ACTIVITY IN THE PREFRONTAL CORTEX. **Cruz-Morales, S.E.**; García-Saldívar, N.L.; González-López, M.R.A.; Domínguez, R.

109. GENETIC DISSECTION OF THE ROLE OF CATECHOL-O-METHYLTRANSFERASE (COMT) IN STRESS REACTIVITY IN MICE. **Papaleo, F.**; Crawley, J.N.; Lipska, B.K.; Weinberger, D.R.; Chen, J.

110. BEHAVIORAL CHARACTERIZATION OF RATS BEFORE AND AFTER LEARNED HELPLESSNESS TRAINING. Padilla, E.; Barret, D.; Rojas, J.; **Gonzalez-Lima, F.**

111. GABA-A RECEPTOR ANTAGONISM MIMICS THE EFFECT OF PROGESTERONE WITHDRAWAL ON FORCED SWIM TEST IMMOBILITY. **Beckley, E.H.**; Finn, D.A.

112. INDIVIDUAL VARIABILITY IN RESPONSE TO PSYCHOLOGICAL STRESSORS IN COMMON MARMOSETS. **Galvão-Coelho, N.L.**; Sousa, M.B.C.

113. ELECTROPHYSIOLOGICAL CHARACTERIZATION OF THE RAT DORSAL RAPHE-CAUDAL LATERAL WING STRESS CIRCUITRY. **Vasudeva, R.K.**; Waterhouse, B.D.

114. BOTH NR2A AND NR2B SUBUNITS OF THE NMDA RECEPTOR ARE CRITICAL FOR LTP AND LTD IN THE LATERAL AMYGDALA OF HORIZONTAL SLICES OF ADULT MICE. **Albrecht, D.**; Müller, T.

Saturday, June 21, 2008

8:30-10:30 ***Symposium 5:*** *Sensory and peptidergic control of food hedonics: Relation to eating disorders.* Chair: Sarah F. Leibowitz.

8:30 RELAPSE TO FOOD SEEKING: ROLE OF CRF, PYY3-36 AND HYPOCRETIN (OREXIN). **Nair, S.G.**; Ghitza, U.E.; Shaham, Y.

9:00 PEPTIDERGIC CONTROL OF FORAGING AND HOARDING. **Bartness, T.J.**; Dailey, M.J.; Keen-Rhinehart, E.

9:30 OVERCONSUMPTION OF FAT: CIRCULATING LIPIDS AND BRAIN NEUROCHEMICALS IN A VICIOUS CYCLE. **Leibowitz, S.F.**

10:00 NEUROTRANSMITTER SYSTEMS IN THE SEEKING AND CRAVING FOR SUGAR AND ALCOHOL. **Hoebel, B.G.**; Avena, N.M.; Rada, P.V.

10:30-11:00 **Break & Exhibit Viewing**

11:00-12:00 **Keynote Lecture, Ian Q. Whishaw,** University of Lethbridge, Alberta Canada. SKILLED FORELIMB USE IN THE RAT AS USED TO MODEL HUMAN NEUROLOGICAL CONDITIONS. Introduction: Melanie Paquette

12:00-2:30 **Break**

2:30-4:30 ***Symposium 6:*** *Transational research on sexual functions: Is it possible?* Chairs: Anders Agmo and Raul Paredes.

2:30 SEX IN MICE AND MEN: BASIC MECHANISMS AND BEHAVIORAL EXPRESSIONS. **Agmo, A.**

2:54 NITRIC OXIDE IN ERECTILE DYSFUNCTION: TRANSLATING PATHOGENETIC CONCEPT INTO THERAPEUTIC APPROACH. **Dugina, J.L.**; Zhavbert, E.S.; Kheyfets, I.A.; Sergeeva, S.A.; Epstein, O.I.

3:18 CHALLENGES OF DEVELOPING PRECLINICAL RODENT MODELS OF SEXUAL MOTIVATION FOR DRUG DISCOVERY PURPOSES. **Deecher, D.**

3:42 CONTROL AND SEXUAL REWARD IN RATS, CAN THAT BE TRANSLATED TO HUMANS? **Paredes, R.**

4:30-5:00 **Break**

5:00-6:00 ***IBNS Business Meeting*** – open to all IBNS members.

6:00-7:00 ***IBNS Fellows Symposium***

This symposium is in honor of Matthew Wayner's 80th birthday, Founding IBNS President. Both Drs. Eisenstein and Oomura are Founding members of the IBNS and are also Fellows of the Society. Introduction: Robert Gerlai.

A BEHAVIORAL HOMEOSTASIS THEORY OF HABITUATION AND SENSITIZATION: CAN IT BE USEFUL IN THE EARLY DIAGNOSIS OF ALZHEIMER'S AND OTHER COGNITIVE DISORDERS? **Eisenstein, E. M.**; Eisenstein, D. L.; Sarma, J. S. M.

PLASTIC EFFECT OF LEPTIN ON THE HIGHER BRAIN FUNCTION. **Oomura, Y.**; Aou, S.; Fukunaga, K.

7:00-11:00 ***IBNS Banquet.*** Awards, buffet, dancing. Harbour Ballroom. DJ – David Sawyer.

Wednesday, June 18, 2008

9:00-10:00 Keynote Lecture: David Amaral

FUNCTIONS OF THE NONHUMAN PRIMATE AMYGDALA AND HIPPOCAMPUS: EVIDENCE FROM LESION STUDIES IN THE DEVELOPING AND MATURE RHESUS MONKEY. Amaral, D. Functions of the nonhuman primate amygdala and hippocampus: evidence from lesion studies in the developing and mature rhesus monkey. ABSTRACT For the past 10 years, our laboratory has been conducting studies designed to define components of the "social brain." These studies involve selective and complete ibotenic acid lesions of the amygdaloid complex; lesions of the hippocampus are produced in lesion control animals. Both groups are compared to sham-operated control animals. All animals have been evaluated on a series of social tasks, tasks of emotional responsiveness and tasks of memory function. Lesions have been produced in mature animals as well as in neonatal animals. For animals with amygdala lesions, no major alteration in the ability to carry out social behavior has been observed. In general, lesioned animals engage in more social behavior rather than less. Adult animals do show a profound change in their expression of fear. They tend to have a blunted fear response both to novel objects and to conspecifics. Recently, we have also shown that the amygdala is necessary for establishing a new fear association although the fear memory appears to be stored in a brain region other than the amygdala. Amygdala lesions in neonates also dampens fear of novel objects but fear within social situations is still apparent. Lesions of the hippocampal formation in adult animals dramatically reduces their ability to use allocentric spatial information to solve a food foraging task. However, if the lesion is produced in neonates, their allocentric spatial mapping ability remains intact. We have also detected long term behavioral changes produced by the neonatal lesions. Both the amygdala and hippocampal groups, for example, have developed patterns of abnormal stereotypical behaviors as adults even though these were not seen for the first two years of life. Interestingly, the types of stereotypies depends on the location of the lesion. I will summarize the major findings of this program of research and draw implications for research on neurodevelopmental disorders.

10:30-12:30 Symposium 1: Stress and anti-stress systems in the regulation of alcohol seeking. Chair: Markus Heilig

THE DIFFERENT ROADS TO ROME: POST-DEPENDENT AND GENETICALLY ENCODED RECRUITMENT OF CRH SIGNALING IN EXCESSIVE ALCOHOL INTAKE AND ALCOHOL SEEKING. Heilig, M.; Hansson, A.C.; Sommer, W.H.; Thorsell, A.; Cippitelli, A.; Ciccocioppo, R. Alcohol dependence, or alcoholism, is a chronic relapsing disorder, characterized by a transition to excessive, uncontrolled alcohol drinking, and a propensity to relapse following extended periods of abstinence. Environmental stressors are powerful relapse triggers in humans, and reinstate alcohol seeking following extinction in experimental animals. Transition from non-dependent to excessive alcohol intake involves long-term neuroadaptations that evolve over years, and require exposure to alcohol. This transition has been modelled in experimental animals. In rats, a prolonged history of dependence characterized by repeated cycles of intoxication and withdrawal leads to induction of long-term behavioral changes, among which excessive voluntary alcohol intake, and increased behavioral sensitivity to stress have been studied in most detail. A recruitment of CRH signaling within the extended amygdala is at the core of this behavioral plasticity. Expression of CRH1 receptors and, to a lesser degree, CRH itself, is long term up-regulated following a history of dependence, while centrally active non-peptide CRH1 antagonists eliminate the behavioral traits of the post dependent state. Work with genetically selected, alcohol preferring mSP rats indicates that the recruitment of the CRH system seen in the post-dependent state can be mimicked by a pre-existing, genetically encoded up-regulation of CRH signaling, resulting in a phenocopy of the post-dependent state. We identified a variant allele of the CRH1-receptor gene in msP rats that is characterized by two SNP markers in the promoter region. In parallel, human data have emerged to indicate that markers within the CRH1 receptor gene are associated with alcohol-related phenotypes. In summary, recruitment of CRH signalling is a major pathophysiological mechanism in alcoholism, and genetic variation within the CRH1 receptor gene may additionally be a pre-existing susceptibility factor. The CRH system and other stress-related neuropeptide systems are candidate targets for developing alcoholism treatments.

YOHIMBINE, A PHARMACOLOGICAL STRESSOR THAT REINSTATES ALCOHOL-SEEKING AND INDUCES EXCESSIVE ALCOHOL INTAKE IN A CRH DEPENDENT MANNER. A.D. Lê, Centre for Addiction and Mental Health, and Department of Pharmacology and Psychiatry, University of Toronto, Ontario. Stress has been implicated as a factor underlying alcohol use and relapse. We have previously shown in rats that exposure to intermittent footshock stress has no effect on alcohol self-administration, but does reinstate extinguished alcohol seeking. Blockade of CRF receptors with d-phe-CRF (non-selective) or CP154, 526 (CRF1 receptor-selective) can attenuate the effect of foothock stress on reinstatement of alcohol seeking. Administration of yohimbine, an alpha-2 adrenoceptor antagonist, which has been shown to induce anxiety-like responses in humans and animals, can also reinstate alcohol seeking in rats. Unlike footshock stress, however, yohimbine also potently enhances alcohol self-administration. We have recently investigated the effects of antalarmin, a selective CRF1 receptor antagonist on yohimbine-induced enhancement of alcohol self-administration and reinstatement of alcohol seeking. Consistent with previous work, pretreatment with the 1.25 mg/kg dose of yohimbine significantly increased alcohol self-administration and reinstated alcohol seeking. Pretreatment with antalarmin at doses of 10 and 20 mg/kg did not affect alcohol self-administration but significantly attenuated both yohimbine-induced increases in alcohol self-administration and reinstatement of alcohol seeking. The results of these studies indicate that the anxiogenic drug yohimbine can stimulate alcohol self-administration and, in a rat relapse model, reinstate alcohol seeking. These effects of yohimbine are mediated at least in part via its actions on the CRF systems. The effect of antalarmin on yohimbine-induced increases in alcohol self-administration parallel its effect on the excessive alcohol consumption observed in alcohol withdrawn mSP rats, selectively bred for high alcohol consumption.

BLOCKADE OF EXCESSIVE POST-DEPENDENT ALCOHOL INTAKE AND STRESS-INDUCED ALCOHOL SEEKING BY NEUROPEPTIDE Y AND NPY-Y2 ANTAGONISM. Thorsell, A; Cippitelli, A; Heilig, M. LCTS, NIAAA, NIH, Bethesda, MD 20892, USA. Neuropeptide Y is an endogenous, anxiolytic neuropeptide that has been extensively examined in behavioral stress and anxiety paradigms. NPY exerts its anxiolytic effect primarily through NPY-Y1 receptors within the amygdala. Based on up-regulated amygdala NPY expression following repeated stress exposure, we proposed that plasticity of the NPY system is a key component in behavioral adaptation to stressors. Consequently, transgenic over-expression of NPY in the rat hippocampus conferred behavioral insensitivity to stress, a phenotype opposite that seen following a history of dependence. Furthermore, exogenous NPY suppresses alcohol intake in animals with a history of ethanol vapor exposure, but not in naïve animals. Amygdala viral vector NPY-overexpression decreased alcohol intake and had a mild anxiolytic effect in rats with a history of dependence. These multiple lines of evidence point to NPY-receptors as candidate treatment targets for high anxiety and/or alcohol intake states. Although agonism at Y1 receptors is an implied therapeutic mechanism, no non-peptide agonists with drug-like properties have been discovered. In an alternative approach, antagonism at the pre-synaptic Y2-receptor may potentiate the release of endogenous NPY, driving Y1-agonism. We demonstrated that BIIE0246, a Y2-antagonist, does indeed suppress alcohol intake in rats, with a sensitization to the antagonist present in ethanol vapor exposed animals. However, BIIE0246 is neither orally available nor brain penetrant. Ongoing work is aimed at preclinically evaluating a novel Y2-antagonist with properties that make it a suitable clinical candidate.

NEUROKININ 1 (NK1) RECEPTOR BLOCKADE: A NOVEL ANTI-STRESS BASED MECHANISMS FOR TREATMENT OF ALCOHOLISM. DT George (1), J Gilman (1), J Hersh (1), A Thorsell (1), DR Gehlert (2), JT Tauscher (2), SP Hunt (3), D Hommer (1) and Markus Heilig, (1); 1: Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD; 2: Lilly Research Laboratories, Indianapolis, IN; 3: Department of Anatomy and Developmental Biology, University College London Behavioral sensitivity to stress increases as alcohol dependence evolves, and stress is a relapse trigger in alcoholism. We have previously demonstrated recruitment of the CRH system as a major mediator of these neuroadaptations, but little is known about possible involvement of other stress mediators. Central substance P released in response to stress acts at neurokinin 1 (NK1) receptors within the amygdala to mediate behavioral stress effects, and thus converges on pathways previously implicated in post-dependent neuroadaptations, but NK1 antagonism has not been examined in relation to alcoholism. We first examined mice with disruption of the NK1 receptor gene, and found that these have markedly decreased voluntary alcohol consumption ($p=0.000001$; appr. 6 vs 10 g/kg/24 hrs at final alcohol concentration), and markedly higher alcohol sensitivity, shown as longer sleep-time following a sedative alcohol dose compared to wildtype littermates (186±14 min vs 104±16 min, $p<0.001$), despite unaltered alcohol metabolism. In anxious, recently detoxified alcoholic inpatients, a novel NK1 antagonist, LY686017, suppressed spontaneous cravings for alcohol (Alcohol Urge Questionnaire, AUQ 3; $p<0.05$) and improved overall well-being (Clinician Global Impression, CGI Severity 4; $p=0.001$) in the absence of effects on anxiety or depression. LY686017 also blunted craving induced by a combined social stress and alcohol cue challenge ($p=0.002$), and attenuated the concommitant cortisol response ($p=0.010$). Finally, brain fMRI BOLD responses to negative affective stimuli (IAPS) were attenuated in LY686017-treated subjects, while responses to positive stimuli were increased. NK1 antagonism represents another approach an anti-stress based treatement that shows a consistent activity profile potentially predictive of clinical efficacy in alcoholism.

5:00-6:30 Oral Session 1: Motivation: Addiction and anxiety. Chairs: Kelly Lambert and Matthew Skelton.

CONTEXT-INDUCED RELAPSE TO HEROIN SEEKING: NEUROPHARMACOLOGICAL MECHANISMS. Bossert, J.M.; Wihbey, K.A.; Koya, E.; Shaham, Y. Behavioral Neuroscience Branch, NIH/NIDA/IRP, Baltimore, MD, 21224, U.S.A. In humans, discrete (e.g., drug paraphernalia) and contextual (e.g., local bar) cues associated with drug intake provoke drug relapse after prolonged abstinence. While the effect of discrete cues on drug relapse in preclinical models has been studied extensively, the effect of contextual cues has been largely ignored. Based on early rat studies of Bouton and Bolles and colleagues on context-induced "renewal" of learned behaviors after extinction, we developed an experimental procedure to study context-induced relapse to drug seeking (Crombag & Shaham, Behavioral Neuroscience, 2002). In this procedure, rats are first trained to self-administer a drug in one context; each drug infusion is paired with a discrete drug cue. Next, the drug-reinforced lever pressing is extinguished in the presence of the discrete cue in a different (non-drug) context that differs from the drug-associated context in term of some combinations of tactile, visual, olfactory, auditory and circadian cues. Subsequently, context-induced reinstatement of drug seeking is assessed by re-exposing rats to the drug-associated context. Using this procedure, we have performed several experiments that have examined the neuropharmacological mechanisms underlying context-induced reinstatement of heroin seeking. Our data suggest that an interaction between dopamine and glutamate transmission in the accumbens shell, the terminal area of the mesolimbic dopamine system, is involved in context-induced reinstatement of heroin seeking. These data and more recent data on the role of dorsal striatum in context-induced reinstatement will be presented at the meeting.

NEURONAL CB2 CANNABINOID RECEPTORS: BEYOND NEURO-IMMUNOCANNABINOID ACTIVITY. Onaivi, E. S., Tagliaferro, P., Brusco, A., Liu, Q-R., Akunne, H., Benno, R., Akinshola, B. E., Arinami, T., Uhl, G. R., and Ishiguro, H. William Paterson University, Universidad de Buenos Aires, Argentina, MNB-NIDA/NIH, Baltimore, MD, Howard University, Washington DC, USA and University of Tsukuba, Japan. The presence and function of neuronal CB2-Rs in the brain had been controversial. We have tackled multiple issues related to the possible roles played by CB2-Rs in the mammalian brain. The direct intracerebroventricular microinjection of CB2 antisense oligonucleotide into the mouse brain reduced mouse aversions in the plus-maze test, indicating the functional presence of CB-Rs in the brain that modifies behavior. Furthermore, we report on the behavioral effects of CB2-R ligands and their influence on food and alcohol consumption in mice, the involvement of CB2-Rs in substance abuse, anorexia and depression in other mouse models and human subjects. We hypothesized that genetic variants of CB2 gene expression may be involved in anorexia, substance abuse and depression. High incidence of the Q63R but not the H316Y polymorphism was found in depression, anorexia and substance abuse in a human population. We also provide the first ultrastructural evidence that CB2-Rs are mainly postsynaptic in the CA1 area of the hippocampus and substantia nigra. Our data demonstrate the functional expression of CB2-Rs in the brain that may provide novel targets for the effects of cannabinoids in the CNS beyond neuro-immunocannabinoid activity.

CB1 RECEPTORS IN THE DORSOLATERAL PERIAQUEDUCTAL GRAY MODULATE DEFENSIVE RESPONSES IN RATS. Lisboa, S.F.S.; Resstel, L.B.M.; Aguiar, D.C.; Guimaraes, F.S. Department of Pharmacology, FMRP-USP, Brazil. CB1 receptors activation by anandamide (AEA) administration into the midbrain dorsolateral periaqueductal gray (dlPAG) induces anxiolytic-like effects in the elevated plus-maze. The aim of this work was to verify if AEA microinjection or facilitation of local endocannabinoid neurotransmission in the dlPAG would also evoke anxiolytic-like effect by CB1 receptors activation in two other models, the Vogel conflict test (VCT) and contextual fear conditioning (CFC). Male Wistar rats (n=5-7) with cannulas aimed at the dlPAG were used. Vehicle or AM251 (CB1-antagonist; 100 pmol/200 nL) was administered into the dlPAG followed, 5 min later, by vehicle, AEA (5 pmol/ 200 nL) or AM404 (an inhibitor of AEA metabolism and uptake, 50 pmol/200 nl). The tests were performed 10 min after the last injection. In the VCT, 24 h water deprived animals were pre-exposed to the apparatus and allowed to drink for 3 min. After another 24 h of water deprivation, they were placed into the apparatus and an electrical shock in the spout of a drinking bottle was delivered at every twenty licks. In the CFC, rats were re-exposed to a context where they had received electrical foot shocks 48 h before the test. Freezing, mean arterial pressure (MAP) and heart rate (HR) were evaluated. AEA and AM404 evoked an anxiolytic-like effect in both tests, with an increased number of punished licks ($F_{5,39}=5.86$, $p<0.0005$ and $p<0.001$, respectively) in the VCT and a reduction of freezing duration ($F_{5, 31}=39.1$, $p<0.001$) and attenuation of the increase in MAP ($F_{1,165}=229$ and 165.2, $p<0.001$, respectively) and HR ($F_{1,165}=379.8$ and 226, $p<0.001$, respectively). AM251 blocked the effects of both drugs ($p<0.05$). These results suggest that an endogenous cannabinoid system in the dlPAG modulates defensive responses. Financial support: FAPESP, CAPES

EFFECT OF PRENATAL EXPOSURE TO NICOTINE AND THC ON FUTURE REWARD PERCEPTION IN C57BL/6J MICE. Fetsko, L.A. Dept. of Biology. The Pennsylvania State University, Schuylkill Campus, Schuylkill Haven, PA 17972 USA Studies have shown that out of the approximately four million women who deliver live births in the United States, about 20.4% say that they have smoked cigarettes at some point during their pregnancy. About 2.9% say that they have smoked marijuana during pregnancy. The general public has the perception that these are not as harmful as other drugs of addiction. The goal of my research is to determine how prenatal exposure to drugs such as nicotine and alcohol will affect the future perception of the rewarding properties of drugs in mice. Conditioned place preference (CPP) was used to assess the rewarding properties of 0.5 and 1.0 mg/kg of nicotine as well as 10% and 25% ethanol in C57BL/6J mice which had been exposed to saline, 0.25 mg/kg, or 0.5 mg/kg of nicotine in utero. The in utero exposure was administered to pregnant females during specific periods of their pregnancy in order to assess critical periods of drug exposure. A pilot test was also run to assess the effect of continuous exposure to vehicle, 5 mg/kg THC, and 10 mg/kg THC and its effect on later perception of THC reward. These experiments involved the use of conditioned place preference and locomotor activity. Results show significant differences between control and experimental animals as well as gender differences with both types of prenatal exposure.

5-HT2A/2C RECEPTORS EXERT OPPOSING EFFECTS ON LOCOMOTOR ACTIVITY IN MICE. [1]Powell, S.B.; [1]Halberstadt, A.L.; [1]van der Heijden, I.; [1]Risbrough, V.B.; [2]Gingrich, J.A.; [1]Geyer, M.A.; [1]University of California, San Diego, La Jolla, CA; [2]Columbia University, New York, NY. Behavioral effects of hallucinogenic drugs have been characterized in animal models to better understand the mechanism of action of these compounds in addition to generating models against which to screen antipsychotic medications. The studies described here using the mouse Behavior Pattern Monitor (mBPM) were designed to test the hypothesis that 5-HT2A and 5-HT2C receptors exert opposing effects on locomotor activity in mice. Our previous studies in C57BL/6J mice indicated that the 5HT2 agonist DOI produces an inverted U-shaped dose response function on exploratory behavior, increasing distance traveled and investigatory holepokes at lower doses and decreasing these measures at higher doses. To examine the contribution of 5-HT2A receptors to the behavioral profile of DOI, we conducted a dose response of DOI in 5-HT2A WT and KO mice on a C57BL/6 background. To examine the effect of 5-HT2C receptor activation on locomotor activity in mice, additional experiments were conducted with 5-HT2C selective compounds. Low doses of DOI (1 mg/kg) increased locomotor activity in 5-HT2A WT mice, an effect that was blocked in 5-HT2A KO mice. Conversely, the decrease in locomotor activity produced by a high dose of DOI (10 mg/kg) was potentiated in 5-HT2A KO mice. The 5-HT2C agonist WAY 161,503 decreased locomotor activity and investigatory holepokes in C57BL/6 mice, effects that were blocked by the 5-HT2C antagonist SER-082. These data suggest that the increase in locomotor activity induced by low doses of DOI is mediated by 5-HT2A receptor activation and that the decrease in locomotor activity produced with high doses of DOI is mediated by 5-HT2C receptor activation. Hence, it appears that 5-HT2A and 5-HT2C receptors exert opposing effects on locomotor activity in mice.

DRUG SAFETY SURVEILLANCE IN CLINICAL TRIALS: THE “NEWER MODEL”. Ostrowski, N.L.; Beasely, C. M. Global Patient Safety, Eli Lilly and Company, Indianapolis, IN 46285 USA The model for drug safety management that continues to evolve relies on the accumulation and evaluation of clinical safety data to inform prescribing physicians and patients about the safe use of newly marketed drugs. Post-marketing safety data are collected, safety signals identified and characterized, and safety recommendations are established for the larger “population” of patients who can benefit from use of the drug. Improvements in this model for drug safety management, as recommended by CIOMS VI and VII, include the continual accumulation and ongoing evaluation of all safety-related data for a new medication beginning with the earliest phases of development. Under this model, companies continue to systematically and cumulatively characterize the evolving safety profile of a new chemical entity, address and minimize safety risks during clinical trials, and proactively clarify conditions for safe use of the drug by patients. This approach reduces the “unknowns” at the time of marketing approval; better describes conditions for optimal safe use by patients; identifies patient subpopulations likely to receive greatest benefit and those for whom benefit may not be proportional to risk; and, consequently, reduces the number of adverse drug reactions experienced by patients during the years following marketing application approval. Greater emphasis will continue to be placed on real-time, periodic, evolving integration of safety data from the multiple sources of such data and explicit, prospective recommendations to minimize safety risks.

Thursday, June 19, 2008

8:30-10:30 Symposium 2: Neuroactive steroids in mental illnesses and drug abuse. Chair: Giovanni Biggio

NEUROACTIVE STEROID-INDUCED MOLECULAR AND BEHAVIOURAL CHANGES DURING SOCIAL ISOLATION STRESS Serra M.; Biggio G. Department of Experimental Biology, Center of Excellence for the Neurobiology of Dependence, University of Cagliari, Italy Rats deprived of social contact with other rats at a young age experience a form of prolonged stress that leads to long-lasting alteration in their behaviour profile. This chronic stress paradigm is thus though to be anxiogenic for these normally gregarious animals and their abnormal reactivity to environmental stimuli, when reared under this condition, is though to be a product of prolonged stress. Neurochemical, molecular and electrophysiological evidence demonstrate that social isolation is associated with alteration in the structure and function of GABAA receptors and suggest that endogenous content of -TH PROG may be an important determinant inα,5αthe progesterone metabolite 3 regulating brain excitability and sensitivity to stimuli and point out its possible role in psychiatric and neurological disorder.

MANIPULATION OF ALLOPREGNANOLONE LEVELS ALTERS ETHANOL SELF-ADMINISTRATION AND REINSTATEMENT IN MALE C57BL/6 MICE. Finn, D.A.; Fretwell, A.M.; Nickel, J.D.; Mark, G.P., Ford, M.M. VA Medical Research & Dept. Behavioral Neuroscience, OHSU, Portland, OR 97239 USA. The present studies examined the modulatory effect of the GABAergic neurosteroid allopregnanolone (ALLO) on ethanol self-administration (10% v/v; 10E) and reinstatement in male C57BL/6 mice. Limited access (2 hr) 2-bottle choice experiments documented that systemic ALLO (3.2 – 24 mg/kg) dose-dependently enhanced 10E onset, while it dose-dependently reduced 10E maintenance. Acute treatment with finasteride (FIN, 50 mg/kg), which decreases endogenous ALLO levels, significantly decreased stable 2 hr 10E intake and reduced 10E onset. FIN (50 or 100 mg/kg) treatment during the acquisition of 10E intake resulted in a significant and dose-dependent rightward shift in the attainment of stable 2 hr 10E intake. In a final study, mice were trained to lever press (single fixed ratio of 16 responses) for 30 min of continuous access to either a 10E or 5% w/v sucrose (5S) solution. Following stable extinction responding, pre-treatment with systemic ALLO (3.2 – 17 mg/kg) produced a dose-dependent reinstatement of non-reinforced responding in both the 10E and 5S groups. This finding indicates that ALLO promotes reinstatement of ethanol and sucrose seeking in male C57BL/6 mice. In conjunction with previous work, ALLO enhances the appetitive and consummatory aspects of self-administration of ethanol and sweet solutions in the mouse.

EFFECTS OF ETHANOL ON GABAERGIC NEUROACTIVE STEROIDS IN RATS AND HUMANS MEASURED BY HIGHLY SPECIFIC GC/MS ASSAY. Morrow, A.L.; de Wit, H.; O'Buckley, T.K.; Alward, S.E.; Porcu, P. Bowles Center for Alcohol Studies, UNC School of Medicine, Chapel Hill, NC 27599 USA. Acute ethanol administration increases 3α-hydroxy,5α-pregnan-20-one (3α,5α-THP) and 3α,21-dihydroxy,5α-pregnan-20-one (3α,5α-THDOC) in rat plasma and brain with mixed effects in human plasma. To determine the effects of all 3α,5α and 3α,5β -reduced GABAergic neuroactive steroids, we developed a highly specific gas chromatography/mass spectrometry (GC/MS) assay. We used this assay to measure serum levels of the GABAergic 3α,5α- and 3α,5β-reduced metabolites of progesterone, deoxycorticosterone, DHEA and testosterone as well the precursors pregnenolone and DHEA. Male rats were injected i.p. with 2 g/kg ethanol or saline and were sacrificed 60 minutes later (BEC,170-190 mg/dl). Acute ethanol administration selectively increased serum levels of pregnenolone, 3α,5α-THP, 3α,5α-THDOC and 3α,5β-androsterone (+589, +191, +291%, $p<0.0001$ and +78%, $p<0.05$, respectively), compared to saline control levels. In contrast, ethanol did not alter 3α,5α-androsterone, 3α,5α-androstandiol, 3α,5β-THP or DHEA levels. 3α,5β-THDOC and 3α,5β-androstandiol were not detected in serum following vehicle or ethanol. Young healthy human males consumed 0.8 g/kg ethanol over 30 minutes and achieved peak BECs of 0.75±0.1 mg/dl. No changes in pregnenolone, DHEA or any 3α,5α- or 3α,5β-reduced GABAergic neuroactive steroid were detected after 60 or 120 min. Studies are underway with lower does of ethanol in rats to evaluate the role of dose in the species differences in ethanol responses. The highly selective GC/MS assay can be used to investigate the physiological and pathological role of GABAergic neuroactive steroids in health and disease.

NEUROACTIVE STEROIDS IN DEPRESSION, PTSD, AND SCHIZOPHRENIA BACKGROUND. Marx, C.; Payne, V.; Keefe, R.; Calhoun, P.; Naylor, J.; Kilts, J.; Hamer, R.; Tupler, L.; Beckham, J.; Morey, R.; Connor, K.; Davidson, J.; Shampine, L. Evidence suggests that neuroactive steroids (NS) play roles in the pathophysiology and therapeutics of depression, PTSD, and schizophrenia, and demonstrate multiple neuroprotective and neurotrophic actions. 1.) We thus determined if serum NS profiles are associated with depression and PTSD symptoms in Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) veterans, and 2.) We conducted a pilot randomized controlled trial investigating adjunctive pregnenolone in patients with schizophrenia targeting cognitive and negative symptoms. METHODS 1.) NS serum profiles were determined by GC/MS or RIA in 90 male OEF/OIF veterans. Assessments included the Beck Depression Inventory-II (BDI-II), Davidson Trauma Scale (DTS), and Symptom Checklist-90-R (SCL-90-R). Canonical correlation analysis to determine if linear relationships exist between predictor variables (NS, smoking, alcohol use, age, h/o traumatic brain injury) and response variables (BDI-II, DTS, SCL-90-R) and subsequent stepwise regression analysis were conducted. 2.) Following a 2-week placebo lead-in, patients with schizophrenia were randomized to adjunctive pregnenolone or placebo for 8 weeks. RESULTS 1.) ALLO levels are inversely associated with BDI-II scores ($p=0.046$) and pregnenolone levels are inversely associated with the SCL-90-R Global Severity Index ($p= 0.049$) in stepwise regression analysis. ALLO/progesterone and DHEA/DHEAS ratios are reduced in veterans with depression ($p=0.0089$ and $p=0.0449$, respectively) or PTSD ($p=0.0316$ and $p=0.0704$, respectively). 2.) Adjunctive pregnenolone significantly reduces negative symptoms in patients with schizophrenia, and serum pregnenolone elevations predict cognitive improvement. CONCLUSIONS 1.) NS are related to psychiatric symptoms in OEF/OIF veterans. ALLO findings are consistent with its antidepressant and anxiolytic actions. Pregnenolone reductions are associated with elevated psychiatric symptoms. 2.) Adjunctive pregnenolone may have therapeutic utility for negative and cognitive symptoms in schizophrenia.

11:00-12:00 Matthew J Wayner-NNOXe Pharmaceuticals Award Lecture - Stephen B. Dunnett

NEURAL TRANSPLANTATION, LEARNING AND RECOVERY OF FUNCTION. Dunnett, S.B. Cardiff University, Wales, UK. We have known for 25 years that neuronal grafts can alleviate both motor and cognitive deficits in animal models of neurodegenerative disease. In recent years our laboratory has sought to develop operant based analyses of lesion and graft function in rats and mice to complement traditional observational, rating, rotometer and maze based tests. In particular, we have focussed on the behavioural analysis of functional recovery associated with embryonic ventral mesencephalic ('nigral') and ganglionic eminence ('striatal') grafts in animal lesion models of Parkinson's and Huntington's disease, respectively. As well as providing a more detailed characterisation of functional deficits and recovery, operant tests have revealed novel (and entirely unanticipated) principles of graft integration and function. This can be illustrated in three sets of experiments: 1. Striatal grafts can restore impairments in operant delayed alternation. Separate lateralised disconnection studies have been used to demonstrate that effective performance on this test is dependent upon the integrity of cortico-striatal circuits, suggesting graft integration into, and true reconstruction of, the damaged brain pathways. 2. In tests dependent upon S-R motor learning in the operant 9-hole box, striatal grafted animals have to 'learn to use their transplants'. This suggests that the transplanted striatal cells need to become reintegrated into host corticostriatal circuits and provide a substrate for the animals to relearn previous motor skills lost as a consequence of the lesions. Corroboration for this hypothesis is provided not only in 'transfer of training' experiments but also in demonstrations of the establishment of physiological plasticity, involving both LTD and LTP, under appropriate conditions in the corticostriatal synapses at the graft/host interface. 3. When we assess animals with nigrostriatal lesions and nigral grafts in the same motor learning tasks, we observe patterns of deficit that appear to suggest recovery, not of a primary motor impairment, as anticipated, but of a progressive impairment, with spontaneous recovery and restitution dependent upon training, which suggests a learning impairment. The pattern of results fit W Schultz' proposal (based on electrophysiological data) that mesencephalic dopamine neurons provide a substrate for signals of reward required to establish and maintain S-R learning, disconnection of which results in lateralised 'extinction'. If so, then the issue of how nigral grafts can provide an effective restitution of reward signalling remains undetermined, but is reminiscent of an earlier demonstration that similar grafts can indeed provide a substrate for intracranial self stimulation. Such insights into graft function, have important implications for the translation of cell replacement therapies to patients. It will not be sufficient to identify suitable sources of cells and transplantation methods for the cells to integrate appropriately at the anatomical level; attention is required to whether we can also provide appropriate rehabilitation in order to maximise the relearning required for the grafts to become functionally effective.

6:00-8:30 Poster Session 1

Animal Models of Human Conditions

1. INACTIVATION OF THE RAT MEDIAL PREFRONTAL CORTEX DISRUPTS RISK-BASED DECISION MAKING. St.Onge, J.R.; Floresco, S.B. Dept. of Psychology and Brain Research Centre. University of British Columbia, Vancouver, BC CAN. Individuals with damage to different subregions of the prefrontal cortex (PFC) display impaired decision making on a variety of tasks requiring cost/benefit evaluations about risks and rewards. However, given the variability in the specific loci of lesions in brain damaged patients, the specific contributions that these regions make to risk-based decision making are unclear. To address this issue, we investigated the role of the prelimbic region of the rat medial PFC (homologous to the human anterior cingulate) in risk-based decision making, using a probabilistic discounting task conducted in an operant chamber. Over daily training sessions, rats chose between two levers; pressing the "Small/Certain" lever delivered one food pellet reward with 100% certainty, whereas choosing the other, "Large/Risky" lever delivered four pellets, but the probability of receiving reward decreased across four blocks of discrete trials (100, 50, 25, 12.5%). Rats displayed stable levels of choice after ~25 days of training, after which they were implanted with bilateral guide cannulae into the medial PFC and subsequently retrained on the task. Inactivation of the medial PFC, via infusions of GABA A/B agonists muscimol/baclofen increased risky choice relative to vehicle infusions, particularly in the latter trial blocks, when it was more advantageous to choose the Small/Certain lever. These findings suggest that this region of the PFC contributes to risk-based decision making by promoting risk-aversive patterns of choice. The fact that damage to this PFC region in humans results in similar risk-prone patterns of decision making suggests that this paradigm may serve as a useful tool in identifying the specific contributions that other regions of the PFC make to risk-based decisions.

2. MESOACCUMBENS DOPAMINE MODULATION OF DIFFERENT FORMS OF BEHAVIORAL FLEXIBILITY. Haluk, D.M.; Floresco, S.B. Dept. of Psychology and Brain Research Centre, University of British Columbia, Vancouver, B.C., V6T 1Z4 Canada. Different forms of behavioral flexibility are thought to be facilitated by interactions between separate regions of the prefrontal cortex and their striatal outputs. However, the contribution that mesoaccumbens dopamine (DA) transmission makes to these functions is unclear. The present study assessed the effects of manipulations of DA receptor activity in the nucleus accumbens (NAc) core on strategy set-shifting and reversal learning, using an automated procedure conducted in an operant chamber. Rats were trained initially on a visual-cue discrimination (i.e.; always press the lever with a light illuminated above it). During the set-shift on the following day, rats had to use a response strategy (e.g.; press the left lever, regardless of the position of the cue) to obtain reward. Infusions of a D1 (SCH23390), but not a D2 (eticlopride) receptor antagonist into the NAc impaired set-shifting, disrupting the acquisition and maintenance of the novel strategy. Conversely, supranormal activation of D2 (quinpirole) but not D1 (SKF81297) receptors also impaired set-shifting, inducing severe perseverative deficits. In contrast, D1 receptor blockade did not affect reversal learning of a response discrimination. These results indicate that mesoaccumbens DA, acting on D1 receptors, selectively facilitates complex forms of flexibility requiring shifts between different strategies. The finding that excessive activation of D2 receptors also disrupts set-shifting suggest that impairments in this executive function observed in disorders such as schizophrenia may be due in part to aberrant increases in mesoaccumbens DA activity.

3. DISSOCIABLE EFFECTS OF BLOCKADE OF NR2A AND NR2B NMDA RECEPTORS ON THE ACQUISITION AND EXTINCTION OF CONDITIONED FEAR. Dalton, G.L.; Floresco, S.B.; Phillips, A.G. Depts. of Psychiatry and Psychology, University of British Columbia, Vancouver, BC, V6J 1K8, Canada. It is well established that NMDA receptor activation is critical for the induction of synaptic plasticity that may underlie the acquisition and extinction of learned fear. Recent evidence suggests that activation of different NMDA receptor subtypes may induce opposing changes in synaptic plasticity with NR2A or NR2B activation inducing LTP or LTD, respectively. Here, we attempted to dissociate the roles of these receptor subtypes in the acquisition and extinction of a Pavlovian fear response. Antagonists selective for NR2A (NVP-AAM077) or NR2B (Ro25-6981) receptors were administered prior to fear conditioning, extinction training or an extinction recall test, each separated by 24-hrs. Neither NVP nor Ro25 affected freezing during conditioning. However, blockade of NR2A, but not NR2B receptors during conditioning resulted in reduced freezing during a fear recall test conducted 24-hrs later. Blockade of NR2B receptors significantly impaired extinction learning, with rats given Ro25 displaying higher freezing levels during the latter stages of the extinction training session. Interestingly, these rats showed no impairment in recall of extinction when tested drug-free 24-hrs later, although blockade of NR2B receptors during the extinction recall test again resulted in higher levels of freezing. In contrast, NR2A receptor antagonism had no effect on the acquisition or expression of extinction. These data suggest that NR2A and NR2B NMDA receptor subtypes may make dissociable contributions to the acquisition or extinction of fear memories, which may be related to the contributions of these receptors to different forms of synaptic plasticity.

4. TRANSLATIONAL RESEARCH IN THE STUDY OF SEXUAL SIDE EFFECTS OF ANTIDEPRESSANTS. Chan, J.S.W.; Olivier, B.; van Hasselt, F.N., Snoeren, E.M.S.; Waldinger, M.D.; Oosting, R.S. Department of Psychopharmacology, Utrecht Institute of Pharmacological Sciences and Rudolf Magnus Institute of Neuroscience, Utrecht University, The Netherlands. The sexual disturbance side effects of selective serotonin reuptake inhibitors (SSRI's) are well documented with up to 80% of depressed patients complaining of sexual dysfunctions. Animal models with a high predictive validity are vital to the study of behavioral neuropsychopharmacology. In previous research, we have found that when Wistar male rats were sexually trained, the rats will fall into consistent and very stable endophenotypes of sexual behavior. When looking at ejaculation numbers, we find consistently that 10% are "slow" with 0-1 ejaculations, 80% are "normal" with 2-3 ejaculations, and another 10% are "fast" with more than 3 ejaculations. Slow and fast ejaculating rats could be possible animal models for human low libido and premature ejaculation disorders, while normal ejaculating rats constitute a group that can be used for testing either inhibitory or facilitating effects of antidepressants. In addition to ejaculations, number of mount and intromissions, and also latencies to all behaviors are examined, generating indications of effects on appetitive behaviors and sexual motivation. We examined 3 antidepressant drugs for sexual behavior effects; venlafaxine, a SNRI, bupropion, a dopamine and noradrenaline reuptake inhibitor, and paroxetine, an SSRI. Acutely, none of the antidepressants affects sexual behaviour. However, after sub-chronic and chronic administration, paroxetine significantly increases latencies to ejaculations and intromissions, number of mounts, and time between ejaculations and resumption of sexual activities. Paroxetine also decreases the number of ejaculations in the 30 minute test. Venlafaxine at lower doses, showed no effects on sexual behaviours. Acutely, Bupropion showed facilitation of sexual behaviour with a significant increase in number of ejaculations compared to vehicle. This facilitation disappears after more treatments with no significant differences compared to the vehicle. Our sexual behaviour test on endophenotypic normal ejaculating rats predicts that bupropion would not induce sexual disturbances in depressed patients.

5. MEASURING IMPULSIVITY IN MICE. GRANON, S.; SERREAU, P.; SUAREZ, S. Integrative Neurobiology of Cholinergic System, CNRS, URA 2182, Pasteur Institute, Paris, France. Impulsive behaviour is frequently observed in psychiatric disorders (Schizophrenia, ADHD, OCD, Addictions) and can be assessed in rats by different tasks. However no behavioural task has been yet specifically developed to measure impulsivity in mice which became essential tools to study the genetic basis of psychiatric disorders. Here we describe the development of such a task. Food deprived mice have to wait for the presentation of a stimulus to make a motor response (a single nosepoke in a single hole) that conditioned the distribution of a food reward. After eating, mice must inhibit its response for a fixed or a variable delay (inter trial interval–iti) before the onset of the next stimulus allowing a rewarded response. An anticipatory response (during iti) reflects impulsivity. We also recorded perseverative responses, response latency and omissions to control for motivation. When the iti got variable and longer, the number of anticipatory responses increased as a function of the iti duration, response latency and omissions decreased while perseverative responses remained unchanged. This new behavioural task allows the measure of impulsivity and offers a precious tool to study this endophenotype in mice models. In addition to the feasibility of this task in any operant box, we designed it for attention to be minimal to avoid any confounding process.

6. GENERATION AND CHARACTERIZATION OF TPH1, TPH2 AND TPH1/TPH2 DEFICIENT MICE. Savelieva, K.V.; Pogorelov, V.M.; Zhao, S.; Rajan, I.; Cullinan, E.; Yang, Q.; Lanthorn, T.H. Lexicon Pharmaceuticals, Inc., The Woodlands, TX, 77381-1160, USA The neurotransmitter serotonin (5-HT) plays an important role in both the peripheral and central nervous systems. 5-HT is synthesized in two steps with tryptophan hydroxylase (TPH) being the rate-limiting enzyme. Until recently it was believed that only one isoform of TPH existed. However, genetic deletion of the known enzyme did not appreciably reduce 5-HT content in the brain, spurring a successful search for an additional enzyme. It is now established that two isoforms exist and tryptophan hydroxylase-1 (TPH1), the long-recognized isoform, controls most peripheral 5-HT synthesis; whereas tryptophan hydroxylase-2 (TPH2) is neuron specific (Cote et al., 2003; Walther et al., 2003). In our study, we used a gene-targeting approach to generate mice with selective and complete elimination of the two known TPH subtypes. This resulted in dramatically reduced central 5-HT levels in TPH2 knockout (KO) and double KO mice; and substantially reduced peripheral 5-HT levels in TPH1 and double KO mice. Surprisingly, despite the prominent and evolutionarily ancient role that 5-HT plays in both vertebrate and invertebrate physiology, none of these mutations resulted in an overt phenotype. Herein, we confirm findings from prior descriptions of TPH1 knockout mice and present the first reported phenotypic evaluations of TPH2 and TPH1-TPH2 knockout mice.

7. LOCOMOTION AND COMPULSIVE CHECKING IN THE QUINPIROLE MODEL OF OBSESSIVE-COMPULSIVE DISORDER (OCD). Silva, C.; McMurran, T.; Vega, V.; Graham, D.; Foster, J.; Szechtman, H. Dept Psychiatry & Behav Neurosciences, McMaster Univ. Chronic treatment with the D2/D3 dopamine agonist quinpirole induces in rats locomotor sensitization and compulsive checking behaviour, a phenomenon that may constitute an animal model of obsessive-compulsive disorder. All current neuroanatomical models of the human disorder propose that OCD represents some dysfunction in a network involving one or more of the cortico-striato-pallido-thalamo-cortical functional loops. Considering that the core subregion of the nucleus accumbens (NAc) is a nodal point in such a network, we examined whether a lesion of it would disrupt the expression of compulsive checking in the quinpirole model. A 2x2 fully crossed factorial design was employed, with one factor being Dose of Chronic Quinpirole Treatment (0 *vs* 0.5 mg/kg) and the other being a Lesion factor (Sham lesion *vs* NAc lesion). After the induction of compulsive checking using our standard protocol, bilateral NMDA lesions were made, and following a 2-wk recovery period checking behavior and locomotion were re-assessed 4 times during the next 17 days; the response to an acute injection of saline/quinpirole was also evaluated. Results showed a very slight reduction in the amount of sensitized locomotion in the lesioned rats but a more marked attenuation in checking behavior. Strikingly, NAc lesions produced marked hyperactivity in saline-treated rats but without yielding compulsive checking. Findings from the animal model are consistent with neuroanatomical evidence implicating the nucleus accumbens as a functionally relevant site in the expression of OCD compulsions.

8. ROTENONE'S EFFECT ON THE GONADAL FUNCTION ON RATS. Martínez-Vega, R.3; Valdez-Pinal, O. 1;Zarraga-Galindo, N.1; Rodríguez-Maldonado, E.4; Ramírez-Escoto, M.2; Rugerio-Vargas, C.2; Vergara-Aragón, P.1; 1Physiology Department, 2Histology Department, Faculty of Medicine, UNAM; 3Mathematics Academy, UACM, SLT, Mexico. 4Nat. Inst. Cardiology. Rotenone is an organic insecticide that has been related with mutagenesis, infertility and congenital malformations on fish and rats. Recently it has been reported that there is a strong link between estrogens and the dopaminergic systems based upon the distribution of receptors and estrogens on neurons that coincide with mesoestriatal dopaminergic paths. The purpose of the present work was to determine the effects of rotenone on the gonadal function on rats. 24 Wistar rats were used; 12 female and 12 male and were divided aleatorily into 2 subgroups; control and experimental by genre. Control subgroups were fed conventionally with Purina Chow; and the experimental subgroups with Purina Chow plus a daily dose of rotenone v.o. (0.2 mg/kg for 21 days). On days 7, 14 and 21 the motor activity was examined on the Open Field Test (OF). On the day 22, animals were housed by pairs to induce the breeding for three consecutive days. 30 days after the breeding, the animals were sacrificed by decapitation and the gonads were fixed in formaldehyde 10% for a tissue analysis with the HE technique. The results showed a decrement on the locomotion of the subjects on the group treated with rotenone, compared to the control group, with no genre difference. The histological analysis did not show morphological differences on the gonads between control and experimental groups. The data suggest that the rotenone could be related with motor control alterations and infertility, associated to a probable state of oxidative stress caused by alterations on the complex I of the mitochondrial chain. Support DGAPA IN221507

9. AN INVERTEBRATE MODEL FOR NICOTINE MOTIVATION. Laurie H. L. Sellings and Derek van der Kooy Department of Medical Genetics and Microbiology, University of Toronto, Toronto, Canada. Although nicotine motivated behaviours have been modeled in nicotine naïve and dependent rodents, it is costly and time consuming to perform genetic analyses in these animals. Conversely, the nematode Caenorhabditis elegans is an ideal genetic model. Since C. elegans exhibits nicotine-induced locomotion resembling that seen in higher organisms, we investigated whether C. elegans might be a good model for nicotine motivated behaviour. To examine whether worms exhibited unconditioned approach behaviour, a chemotaxis assay was conducted using standard 100 mm Petri dish containing 6 ml of chemotaxis agar with a spot of concentrated nicotine at one side allowed to diffuse 3-16 h. Then, 50-200 worms were placed in the centre, and their location relative to the spot recorded 15-120 min later. Worms approached nicotine in a concentration-, time-, and age-dependent manner. Approach was attenuated or eliminated in worms with mutated nicotinic receptor subunits; however, approach to the volatile attractant benzaldehyde was left intact. This model of nicotine motivated behaviour could translate into an efficient screen in the identification of genes implicated in the development and maintenance of nicotine dependence. Supported by CIHR and CTCRI grants. LHLS holds postdoctoral fellowships from CIHR and the CIHR Tobacco Use in Special Populations program.

10. EFFORT-DRIVEN REWARDS AND LEARNED PERSISTENCE: A NOVEL ANIMAL MODEL FOR BUILDING RESILIENCE AGAINST DEPRESSION. Hyer, M.; Crockett, A.; Rzucidlo, A.; Kuehn, J.; [1]Hawley, D.F.; Lambert, K.G. Dept of Psychology, Randolph-Macon College, Ashland, VA 23005; [1]Dept of Psychology, University of Houston, TX 772204 The effort-driven reward (EDR) circuit emphasizes the integrative relationship among the nucleus accumbens, striatum and prefrontal cortex as an underlying mechanism for many symptoms of depression (e.g., anhedonia, difficulty concentrating, motor fatigue, sadness); additionally, it has been suggested that EDRs mitigate the stress response that is known to contribute to the onset of depression (Lambert, 2005). The present study replicated previous findings in our lab examining persistence in a problem solving task in EDR trained animals that were required to dig in mounds of bedding for froot loop rewards every day for four weeks. These animals were later exposed to a novel persistence task, providing an assessment of persistence within the allotted task duration. In a prior study, animals receiving EDR training exhibited learned persistence by spending more time "on task" attempting to retrieve the food reward. In the current study, although both effort-driven reward and control rats were matched for emotionality prior to EDR training, nonsignificant trends were observed in the final persistence test; specifically, effort-driven reward rats had shorter latencies to approach the novel task ($p=.06$) and longer average contact durations trying to retrieve the food reward ($p=.07$) than their non-trained counterparts who had equal exposure to the testing environment and received the same number of froot loops in a non-contingent manner. In addition to the problem-solving challenge, animals were exposed to an ecologically relevant stressor to investigate fecal corticosterone levels in both groups (these data are still being processed.). In sum, in an alternative version of learned helplessness, this study suggests that the exploration of learned persistence and effort-driven rewards present an opportunity to explore resilience-building strategies in rodents.

11. EFFECTS ON A RAT MENOPAUSE MODEL OF AN ALIMENTARY COMPLIMENT BASED ON A BEE PRODUCT. Zarraga-Galindo, N.1; Meléndez-Rosales, S.; Martínez-Vega, R.3; Valdez-Pinal, O. 1; Palacios-Heredia, M.R.; Rodríguez-Maldonado, E.4 Ramírez-Escoto, M.2; Rugerio-Vargas, C.2; Vergara-Aragón, P.1; 1Physiology Department, 2Histology Department, Faculty of Medicine, UNAM; 3Mathematics Academy, UACM, SLT, Mexico. 4Nat. Inst. Cardiology Oophorectomy often comes with organic changes that can be partially associated to a depletion on the estrogen levels. Preliminary studies have reported that bee products like Royal Jelly prevent osteoporosis on oophorectomized rats as an effect of the testosterone and steroid hormones (Hidaka, 2006). The present work was realized to determine the effects of an alimentary compliment based on bee products (pollen, honey, royal jelly, bee wax and drone and bee queen larvae) on the bodyweight, food consumption, motor activity, hormonal profile and an histological analysis of the gonads. Design: 24 Wistar female old rats were used. Animals were randomly divided into 3 groups of 8 rats each: 1)Control-Sham group; 2)Oophorectomized rats (fed conventionally), no treatment; 3)Oophorectomized rats like above plus bee product treatment. Bodyweight, Open Field Test (OFT) and the alimentary consumption were determined. At the end, animals were sacrificed by decapitation, estrogen levels were determined. Results: The groups 1 and 2 showed a progressive increment on bodyweight and a decrement on the amount of squares crossed on the OF. Meanwhile, group 3, showed a progressive decrement on the bodyweight and an increment on the amount of squares crossed on the OFT. The groups 1 and 2 compared to group 3 showed differences on the morphometric parameters. Probably the frequent consumption of bee products on a convetional diet on oophorectomized rats provides an increment on motor activity and a low bodyweight. Support DGAPA INN2215107

12. XENON AND NITROUS OXIDE NEUROPROTECTION AGAINST TRANSIENT FOCAL CEREBRAL ISCHEMIA IN RATS: FUNCTIONAL RECOVERY REQUIRES SEVENTY FIVE PERCENT OF IPSILATERAL CORTEX INTEGRITY. Haelewyn, B.; Rouillon C. and Abraini J. NNOXe Pharmaceuticals, 3107 Avenue des Hôtels, Suite 18C, Québec, QC G1W 4W5, Canada. Brain damage that follow disruption of regional cerebral blood flow is the most common cause of permanent disability and is associated with a high incidence of sensory, motor and cognitive deficits. Among the various strategies studied to improve the vital prognostic of patient, nitrous oxide and xenon have been recently demonstrated to afford tissue neuroprotection in various in vitro and in vivo models and to enhance sensory and motor recovery measured by rearing activity and motor coordination. Indeed, in rats subjected to intraluminal transient focal cerebral ischemia, xenon and nitrous oxide at non-anesthetic concentrations (37.5-75 vol%) during 3h offer powerful cortical neuroprotection and functional recovery when administered up to 2 h, but not 3 h, after ischemia onset (David et al., 2003; David et al., 2007; Haelewyn et al., 2008). Besides, using these data, we show that histological neuroprotection induced by xenon and nitrous oxide requires being sufficiently important to preserve about 75 % of the ipsilateral cortex subjected to ischemia in order to provide improvement of neurologic outcome. By contrast, in our conditions where subcortical structures are not protected by nitrous oxide or xenon, correlations between brain damage and behavioural tests involving the motivation fail to reveal any implication of striatum in neurological recovery. This should be taken into account in preclinical pharmacological studies to estimate the actual potentially clinical interest of drugs developed for neuroprotection.

13. BMY-14802 AS A NOVEL ANTI-DYSKINESIA TREATMENT: SUPPORT FROM A BEHAVIORAL BATTERY IN THE 6-OHDA RAT. Paquette, M.A.; Foley, K.E.; & Berger, S.P. Laboratory of Translational Behavioral Neuroscience, Oregon Health & Science University and the VAMC, Portland, OR 97239 The unilateral 6-hydroxydopamine (6-OHDA) rat model of Parkinson's Disease has been used to test pharmacotherapies for L-DOPA-induced dyskinesia (LID). However, few studies have included thorough behavioral assessment to investigate whether these pharmacotherapies selectively suppress LID without suppressing the therapeutic effects of L-DOPA. Furthermore, behavioral tests should be used to determine whether anti-LID pharmacotherapies might themselves have therapeutic effects. Therefore, we have assembled a behavioral test battery, including the Vibrissae-Stimulated Forelimb Placement (VSFP), Cylinder, Paw Placement, Elevated Body Swing, and Grip Release tests. This battery was used to investigate the putative anti-LID agent BMY-14802. At baseline, rats showed no asymmetries in performance on any of the behavioral tests. After the lesion, rats showed increased contralateral misses on the VSFP, decreased contralateral use in the Cylinder and Paw Placement, decreased contralateral Elevated Swing, and decreased preference to release the contralateral paw first in Grip Release. Our preliminary data demonstrate that L-DOPA improved performance on the VSFP, Cylinder, Elevated Swing, and Grip Release tests. However, performance in the Cylinder was confounded by LID. BMY-14802 improved performance on the Elevated Swing and Grip Release tests. BMY-14802 did not suppress L-DOPA's therapeutic effects in the VSFP. By suppressing LID in the Cylinder, BMY-14802 improved performance to baseline levels. Therefore, BMY-14802 might be an effective anti-LID treatment in human patients and may itself have therapeutic effects. Supported by VA Merit #07-1003.

14. A DOPAMINE DELIVERY STRATEGY WITH NANOCARRIERS ON A RAT HEMIPARKINSONISM MODEL INDUCED BY 6-OHDA. VERGARA-ARAGON, P.1; MARTÍNEZ-VEGA, R.2; PALACIOS H., M.R.1; VALDEZ P., O.1; ZARRAGA G., N.1 1Physiology Department, Faculty of Medicine, UNAM, 04510; 2Mathematics Academy, UACM, Sn Lorenzo Tezonco, Mexico. TiO2 (Titania) nanoparticles have been implanted on the caudate nucleus to deliver dopamine (DA) continuously on a rat hemimiparkinsonism model induced by 6-OHDA. The purpose of the study was to examine its effectiveness on the reversion of the gross motor alterations caused by dopamine depletion in the nigrostriatal bundle. Gross motor behavior was registered on the Open Field (OF) and Cylinder Task (CT) (during 5 min), and Girus behavior (G), induced by apomorphine, was registered for 50 minutes. 32 Wistar rats (250g) were divided into four experimental groups (8 rats each) as follows: 1) Control group, no treatment and surgery sham; 2) Unilateral lesioned rats (6-OHDA); 3) Unilateral lesioned rats with nanocarriers implanted without treatment; 4) Unilateral lesioned rats with nanocarriers implanted with DA. Every group was examined on the behavioral tests listed above. The results showed that the rats treated with DA didn't have significant differences with the control group on the OF, CT and G. While the group with nanocarriers implanted without DA showed no difference from the group with unilateral lesioned rats, however both groups were significant different from the other two (control and DA nanocarriers). It is probable that the continuous release of dopamine through the nanocarriers is capable of reversing the motor deficit observed on the lesioned group. This type of reservoir can be a promising controlled drug delivery system to treat the Parkinson disease with and will be evaluated on Wistar rats in a future work. Support Contributed By: DGAPA IN-221507

15. OXIDATIVE STRESS INDUCES NEUROINFLAMMATION AND PROGRESSIVE NEURODEGENERATION IN HIPPOCAMPUS OF RATS EXPOSED TO OZONE Rivas-Arancibia S; Guevara-Guzmán R; Flores-Rodríguez T; López-Vidal Y. Departamento de Fisiología y Departamento de Microbiología, Facultad de Medicina. UNAM. México, D.F. The purpose of this study was to determine the effects of oxidative stress on inflammatory response, and its relation with rats´ progressive neuronal death in the hippocampus. 70 Wistar male rats were divided into 5 groups (n=14) and each group received one of the following treatments: 1) Control; 2) Ozone (O3) for 15 days; 3) O3 for 30 days; 4) O3 for 60 days; and, 5) O3 for 90 days. Ozone exposure was for 4 hours daily, 0.25ppm. 2 h after each treatment had finished, animals were tested in a passive avoidance test in order to measure short-term memory. Afterwards, ten animals were deeply anesthetized and dead by decapitation. The hippocampus was dissected to quantify lipid peroxidation levels using immunblot techniques. Four rats were perfused and their brains obtained by immunohistochemistry techniques for p53, tumoral necrosis factor alfa (TNF-α), Microglia, Glial Fibrillary Acidic Protein (GFAP) and inducible Oxide nitric synthase (iNOS). Immunoreactive cells were then counted. Results showed short-term-memory alteration, lipid peroxidation levels increase depending on the time to ozone exposure compared to those of the control group. In the immunoblot test and immunohistochemistry, we found that there is an increase in relation to time of exposure in p53 and iNOS at 7 and 15 days; GFAP and Microglia at 15 and 30 days; TNF- α at 60 and 90 days. This increase remains during 90 days of ozone exposure. In conclusion, oxidative stress state induced the temporal expression of different inflammatory markers during the progressive neurodegeneration process in the hippocampus. Supported by DGAPA IN215408 to S.R-A and SDI05.5 to R.G-G

16. OXIDATIVE-STRESS EFFECTS OVER EXPRESSION OF FOXO3A IN THE INFLAMMATORY RESPONSES IN RAT'S HIPPOCAMPUS EXPOSED TO OZONE. Moreno-Bernal A; Sanchez-Vega R, Gonzalez-Rivas D; Borgonio-Perez,G; Rivas-Arancibia S. Departamento de Fisiología, Facultad de Medicina. UNAM, México, D. F. FoxO proteins are a subgroup of the Forhead family of transcription factors; they have a crucial role in cellular processes: regulate apoptosis, cell cycle progression, oxidative-stress resistance and immune homeostasis. One subgroup of them is FoxO3a that protect quiescent cells from oxidative stress by increasing expression of manganese superoxide dismutase. In our laboratory we have showed that ozone exposure at low doses for long time caused oxidative stress and death cell in hippocampus. The purpose of this study was determine the effects of oxidative stress on FoxO3a expression and the participation on inflammatory response in rat's hippocampus exposed chronically to ozone. Fifty Wistar male rats were divided into 5 groups (n=10) each group received one of the following treatment: 1) Control (air stream free of ozone), 2) Ozone for 15 days, 3) Ozone for 30 days, 4) Ozone for 60 days and 5) Ozone for 90 days. Ozone exposure was for 4h daily, 0.25ppm. Two hours after to the last exposure to ozone animals were deep anesthetized and perfuse, so their brains were processed for immunohistochemistry techniques against: Forkhead box 3a (FoxO3a), Bcl2, Nucelar Factor kB (NFkB). Results showed that FoxO3, NFkB and Bcl2 increases at 7 to 15 days, and the immunoreactivity was falling in hippocampus 30, 60 and 90 days. The Citochrome C cell number increase on all group in relation to time of exposure. In conclusion, the neurodegeneration process caused by oxidative stress the expression of FoxO3a and Bcl2 appear at the beginning of inflammatory response when the cells damage can be reverted. Supported by DGAPA IN215408 to S. R-A

17. EFFECT OF OXIDATIVE STRESS ON RAT HIPPOCAMPUS CHRONICAL EXPOSURES TO LOW OZONE DOSES. Rodriguez-Martínez E.; Sánchez-Vega R.; González-Rivas S.; Borgonio-Pérez G.; Rivas-Arancibia S. Departamento de Fisiología, Facultad de Medicina. UNAM, México, D. F. In an oxide-reduction balance, oxidative signals are involved in brain repair. When a chronical oxidative stress state is present, the brain cells lose the capacity to restore. In our laboratory, we demonstrated that ozone exposure at low doses for long time causes an oxidative stress state, which leads to progressive cell death. The purpose of this work was to study the effects of oxidative stress on neurogenesis process, mitochondrial alteration, and progressive neuronal death in the hippocampus of rats exposed to ozone. Thirty Wistar male rats were divided into six groups (n=6); each group received one of the following treatments: 1) Control; 2) Ozone (O3) for 15 days; 3) O3 for 30 days; 4) O3 for 60 days; and, 5) O3 for 90 days. Ozone exposure was for 4h daily, 0.25ppm. Two hours after each treatment had finished, animals were deeply anesthetized, perfused and their brains obtained for immunohistochemistry techniques against nitro-tyrosine (NT), double cortine (DXC) proliferating cell nuclear antigen (PCNA), PPARPγ coactivator-α1 (PGC-1α), and neuronal nuclei (NeuN). Results showed an NT increase in relation to time of exposure. We also found increases in DXC and PCNA at 15 days, while PGC-1α and Neu N decrease during all time of exposure to ozone. In conclusion, oxidative stress per se induces a neurogenesis process loss associated with a mitochondrial biogenesis alteration and cellular death which altogether induce a progressive neurodegeneration process similar that occur during Alzheimer's disease. Supported by DGAPA IN215408 to S. R-A

18. STRIOSOME AND MATRIX PATHOLOGY AND MOTOR DEFICITS IN THE YAC128 MOUSE MODEL OF HUNTINGTON'S DISEASE. Lawhorn, C.; Smith, D.M.; Brown, L.L. Huntington's disease (HD) is a neurodegenerative movement disorder caused by an abnormally expanded CAG repeat. The major site of pathology in HD is the striatum. The striatum is compartmentalized into striosomes, which in rodents are mu opioid receptor-rich and calbindin-poor clusters of cells embedded in an extrastriosomal matrix. In early stages of HD there is evidence that the striosome compartments may be more vulnerable to degeneration than the surrounding matrix. To determine the presence of compartment-specific pathology and its relation to motor symptoms we tested 7, 10 and 13 month YAC128 transgenic mice versus wild types (WT) on motor tasks and used unbiased stereology and 3D reconstructions to evaluate pathology in striosomes versus matrix. Compared to WTs, 13 month YAC128s showed selective volume shrinkage in striosomes and cell loss in both striosome and matrix compartments. There was a greater percentage of cell loss to striosomes than matrix. YAC128s also had rotarod and balance beam deficits that preceded volume and cell loss. At 13 months balance beam slips and striosome cell number were inversely correlated. The results show that pathology in older YAC128s can manifest as an abnormal ratio of striosome to matrix volume and cell number, which may contribute to motor symptoms, especially for balance beam slips.

19. TIME COURSE FOR MEMANTINE NEUROPROTECTION IN AN NMDA NUCLEUS BASALIS LESION MODEL OF NEURODEGENERATION IN RAT: Curzon,P.;Markosyan,S.;Nikkel,A.L.;Salte,K.; Bitner,R.S.; Decker,M.W. Neuroscience Research,Abbott Laboratories,Abbott Park,Illinois 60064 Early studies demonstrating the neuroprotective effects of memantine (MEM) administered immediately following NMDA lesions to the Nucleus Basalis (NBM) of rats were important in bringing forward this compound for clinical development. However, as MEM is a potent NMDA antagonist, the neuroprotection it affords may be mostly the result of pharmacological antagonism of the NMDA receptors at the time of injection. Effects on later stage neurodegeneration processes cannot be assessed under these conditions. An experiment was therefore conducted in which administration of MEM was delayed following a unilateral injection of NMDA (60nmol in 1 µl PBS) into the NBM of adult Wistar rats. These lesions produce a 35 – 50 % cholinergic fiber loss in cortical regions. Six groups of rats were used; NBM PBS injected with saline or with 10 mg/kg of MEM at the time of surgery, or, NMDA lesioned rats with MEM injected 1, 3 or 6 hr post lesion. BID injections were made for 2 additional days. Deficits in behavior were assessed using novel environment locomotor activity (LA), novel object recognition (NOR) and inhibitory avoidance (IA) tests beginning 4-5 days after the lesion. Following testing brains were examined histologically to count cholinergic fibers. No adverse effects of either the lesion or MEM treatment in LA were observed. However, there was a significant NOR reduction following the lesion and a significant reversal by MEM treatment given 1 hr post lesion but not at 3 and 6 hr. A similar effect was seen in IA. MEM is therefore neuroprotective when administered 1 hr post lesion but not at 3 hr post lesion.

20. OREXIN (HYPOCRETIN) GENE TRANSFER IMPROVES NARCOLEPTIC SYMPTOMS IN OREXIN NULL MICE. Liu, M.; Thankachan, S.; Kaur, S.; Begum, S.; Blanco-Centurion, C.; Sakurai, T.; Yanagisawa, M.; Neve, R.; Shiromani, P.J. Narcolepsy is a neurodegenerative disorder linked to the loss of orexin neurons. A behavioral phenotype that resembles narcolepsy occurs in mice when the orexin gene is deleted. Gene transfer has proven to be an effective neurobiological tool in a number of neurodegenerative diseases but it is not yet known if it can also correct a sleep disorder. Here, a HSV-1 vector was constructed to test if orexin gene transfer could reverse the symptoms of narcolepsy in orexin knockout mice with narcolepsy phonotype. First, in-vitro tests (PCR and immunohistochemistry) confirmed expression of the gene in cultured cells. Then the time-course of expression was confirmed by delivering the vector into the lateral hypothalamus (LH) of orexin knockout mice. Lastly, the vector was placed into the LH of orexin knock out mice (n=13) and effects on sleep-wake were assessed. Control mice (n=9) received the GFP vector. Sleep was also recorded from wildtype (WT) mice (n=9) of the same background strain (C57BL/6J) and age (3-7 months old; 20-35 g) as the orexin knockouts. Numerous orexin-A immunoreactive neurons in the LH of orexin knockout mice were evident 1-3 days after gene transfer followed by a decline after the 4th day. Orexin gene transfer into the LH decreased the incidence of cataplexy by 60% (versus control vector), and the levels of REM sleep during the second half of night were same as WT. HSV-1 vector-based orexin gene transfer reorganized and improved REM in knockout mice. This methodology provides an efficient tool to determine how sleep becomes reorganized in an animal model where the underlying network exists but the sleep abnormality results from a missing gene. Support: NIH grants (NS030140, NS052287) and VA Research Service

21. THE EFFECTS OF PRENATAL INFLAMMATION ON THE DEVELOPMENT OF MOTOR AND SOCIAL BEHAVIORS, IN JUVENILE MALE AND FEMALE RATS: IMPLICATIONS FOR THE STUDY OF NEURODEVELOPMENTAL DISORDERS. Evelyn F. Field, Scott A. McLeod, Quentin J. Pittman, Hotchkiss Brain Institute, Department of Physiology and Biophysics, Faculty of Medicine, University of Calgary, Calgary, AB Canada Maternal infection during gestation is a risk factor, in humans, for neurodevelopmental disorders such as autism and schizophrenia. Both autism and schizophrenia are associated with impairments in motor, sensory and cognitive function that may differ developmentally between males and females. What is not known is whether behavioral deficits are present during the juvenile period in animal models in offspring exposed to inflammation prenatally, via the dam. In the present study we gave Long-Evans female rats, on gestational day 16 either, saline, 50 or 100 µg/kg of lipopolysaccharide (LPS) to activate the maternal innate immune system. Male and female juvenile offspring were tested for changes in anxiety, overall activity, motor coordination, and play behavior. We found that both male and female offspring exhibited impairments in motor coordination during a reflexive righting task. During play behavior only LPS exposed females were less likely to respond to the initiation of a playful attack. Thus, the development of the neural systems underlying the expression of these behaviors, in males and females, may be differentially affected by maternal immune system activation. Furthermore, this work shows that changes in behavior, as a result of exposure to inflammation in utero, can be found prior to puberty, a finding that has not been previously documented using this animal model. These results are relevant for the study of sex differences in the development, prevalence and symptoms of neurodevelopmental disorders such as autism and/or schizophrenia. Research support from AHFMR, CIHR.

22. ROLE OF NOREPINEPHRINE IN CRF-INDUCED DEFICITS IN SENSORIMOTOR GATING. Gresack, J.E.; Wallace, C.; Geyer, M.A.; Risbrough, V.B. Dept. of Psychiatry, Univ. of Calif. San Diego, La Jolla, CA 92093-0804 USA. Prepulse inhibition (PPI), defined as the inhibition of the acoustic startle reflex (ASR) resulting from presentation of a non-startling stimulus (prepulse) prior to a startling stimulus, is an operational measure of sensorimotor gating and is disrupted in some neuropsychiatric disorders. Some of these disorders (e.g. post-traumatic stress and panic disorders) have also been shown to have alterations in corticotropin-releasing factor (CRF) systems. CRF, a neuropeptide released in response to stress, increases ASR and reduces PPI in rodents. The neurotransmitter mechanisms mediating CRF modulation of ASR and PPI are unknown, though evidence suggests involvement of the norepinephrine (NE) system. CRF increases NE release and NE modulates ASR and PPI. Activation of the α_1 receptor disrupts PPI, an effect blocked by the presynaptic α_2 agonist, clonidine. Here we tested the hypothesis that NE release mediates CRF disruptions of ASR and PPI. C57BL/6 mice were pretreated with clonidine (0.09 mpk, ip) or saline 30 min before and 1 hr after oCRF (0.6 nmol, icv) infusion. Testing occurred 2 hr after oCRF infusion. oCRF increased ASR and this effect was attenuated by clonidine. Nevertheless, clonidine did not reverse CRF disruptions in PPI. These data suggest that CRF-induced increases in ASR may require release of NE. The selective effect of clonidine on CRF-induced changes in ASR, but not PPI, also suggests that neurotransmission mechanisms mediating CRF changes in startle reactivity may be dissociable from CRF changes in startle plasticity (PPI). Future studies will explore postsynaptic NE involvement in CRF effects on ASR and PPI. Support: NIH MH074697

23. DEFICITS IN PREPULSE INHIBITION INDUCED BY STIMULATION OF THE LOCUS COERULEUS ARE REVERSED BY BLOCKING NOREPINEPHRINE, BUT NOT DOPAMINE OR SEROTONIN RECEPTORS. Alsene, K.M.; Ramaker, M.J.; Schwerin, L.M.; Bakshi, V.P. Dept. of Psychiatry & Neuroscience Training Program, UW-Madison, Madison, WI USA. Prepulse inhibition (PPI) refers to the ability of a weak pre-stimulus to inhibit the magnitude of the startle response to a subsequent intense stimulus. PPI is a measure of sensorimotor gating, or the ability to filter information from the internal and external environment, and is deficient in several psychiatric illnesses, including schizophrenia. There is emerging evidence indicating that increasing central norepinephrine (NE) transmission disrupts PPI. Our lab recently found that pharmacological stimulation of the locus coeruleus (LC), the primary source of NE to the forebrain, disrupts PPI. However, it is possible that the disruption in PPI induced by LC stimulation is due to interactions between the monoamine systems. Therefore, the present study tested the hypothesis that the PPI-disruptive effects of LC stimulation would be prevented by blocking either NE, dopamine, or serotonin receptors. Separate groups of rats were tested for PPI after being pretreated with either the norepinephrine (α1 receptor) antagonist, prazosin (N=11), the dopamine (D2 receptor) antagonist haloperidol (N=11), or the serotonin (5-HT2 receptor) antagonist, ritanserin (N=7) prior to receiving peri-LC infusions of the cholinergic agonist, bethanechol. In all the groups bethanechol alone significantly disrupted PPI, replicating our previous finding that LC stimulation disrupts PPI. Prazosin completely blocked this effect whereas neither haloperidol nor ritanserin had any effect. Thus, it appears that the ability of LC stimulation to disrupt PPI is mediated by putative downstream release of NE but not dopamine or serotonin. This indicates a novel, distinct, dopamine- and serotonin-independent pathway in the regulation of PPI.

24. DIFFERENTIAL EFFECTS OF A D1 ANTAGONIST IN SOCIAL BEHAVIOUR AND FEEDING Gray, D.G.; Irwin, J.; Mittelholtz, J.; Choleris, E. Dept. of Psychology. University of Guelph, Guelph ON,Canada. Several motivated behaviours (e.g. feeding, mating and drug addiction) are regulated by the dopaminergic system. Dopamine (DA) modulation via the D1 and D2 receptor families have been shown to also effect social behaviour, including aggression, social interactions, and social bonding. Whether these receptors are similarly involved in the modulation of feeding and social hierarchies in rats and mice, is still unknown. We investigated the effects of a selective D1 receptor subfamily antagonist SCH23390 on the feeding and social responses of adult male rats and female mice. Animals received either a LOW (0.01), MED (0.05), or HIGH (0.1) mg/kg dose, or were uninjected (UNINJ). Intraperitoneal injections were delivered to one of a dyad of familiar conspecifics, (RATS 20 min, MICE 15 min) prior to a 30 min videotaped social interaction. Following the social interaction, treated rats were given a 24h feeding test with ground rodent chow. An ethological assessment was performed on the behaviour of the treated animals during the social interaction. Behaviours were scored and grouped according to the following categories: social aggression received, social aggression delivered, social investigation (non-antagonistic), non-social activity, inactivity, and abnormal stereotypical behavior. In RATS all doses of SCH increased non-social behaviour while attenuating the rats engagement in social behaviour. Conversely, in MICE only the MED and HIGH doses significantly decreased non-social behaviour after the initial 5 min of the social interaction. In MICE all doses of SCH failed to reveal a significant effect on the overall level of social behaviour across treatment groups. SCH-treated RATS displayed significant attenuation of social investigation and total aggressive behaviours. SCH-treated RATS also demonstrated an increase in submissive behaviour (vs. controls) as well as a proportional increase (correlated for overall activity) in aggressive behaviour received via the cagemate. SCH-treated MICE also displayed significant attenuation of social investigation, but failed to demonstrate any effect on submissive or aggressive behaviour. In RATS, but not in MICE, injection/handling reduced overall levels of activity during social interaction. There was not any significant difference of overall activity between control groups in MICE. In RATS, but not in mice, SCH attenuated food consumption. Overall, we have shown that only SCH in RATS may interfere with motivation to feed and may be involved in the formation of dominance hierarchies via SCHâ€™s effects on aggression. These results may either reflect differential response, in the two rodent species, to the same doses of SCH or previously not described species differences in the involvement of the D1 receptor subfamily in feeding and social behavior.

25. COMPREHENSIVE BEHAVIORAL PHENOTYPING OF NEUROLIGIN 3 R451C KNOCKIN MICE. Chadman, K.K.1; Gong, S.2; Scattoni, M.L.1; Boltuck, S.1; James, J.2; Kus, L.2; Heintz, N.2; Crawley, J. N1. 1Laboratory of Behavioral Neuroscience, IRP, NIMH, Bethesda, MD 20892-3730; 2GENSAT Project, Rockefeller University, New York, NY 10021. Neuroligins are postsynaptic neural cell adhesion molecules that bind to presynaptic neurexins and are thought to contribute to the functional development of synapses. Mutations in neuroligin 3 were reported in 2 brothers with autism spectrum disorders (Jamain et al., 2003). Autism is a neurodevelopmental disorder diagnosed by 1) aberrant reciprocal social interaction, 2) impaired communication, and 3) stereotyped and repetitive behaviors with narrow, restricted interests. The mutant (R451C) neuroligin 3 gene was knocked in using BAC mediated gene-targeting in ES cells. Infant, juvenile and adult mice were characterized on social tests, learning and memory and reversal tasks, and control measures of general health, sensory abilities, and motor functions. NL3 R451C knockin mice displayed normal scores on measures of pup vocalizations, juvenile play and adult social approach. Genotypes did not differ on Morris water maze acquisition and reversal, or on standard delay contextual and cued fear conditioning. While no differences were detected in general health, open field, prepulse inhibition, or pain sensitivity, NL3 mice displayed deficits in the development of the righting reflex, adult acoustic startle reactivity, swim speed and thigmotaxis during Morris water maze testing, and lower vertical activity in the open field. These findings do not support the interpretation of an autism-like phenotype in NL3 knockins, but suggest the R451C mutation may lead to lower arousal levels in mice.

26. FUNCTIONAL $GABA_B$ RECEPTOR CHANGES ASSOCIATED WITH THE MATERNAL *FMR-1* GENOTYPE IN THE MOUSE MODEL OF FRAGILE X SYNDROME. Zupan B.[1] and Toth M.[1,2] [1]Graduate program in Neuroscience; [2]Pharmacology Department, Weill Graduate School of Medical Sciences of Cornell U., New York, NY. Fragile X syndrome is an X linked disorder caused by the inactivation of the FMR-1 gene with symptoms ranging from impaired cognitive functions to seizures, anxiety, sensory abnormalities and hyperactivity. Although Fragile X syndrome is considered a typical genetic disorder, we have recently described that the environment, specifically the maternal environment, also contributes to the disease phenotype in *fmr-1*$^{-/0}$ (KO) male mice. We showed that the hyperactivity phenotype in KO mice is not only dependent on the subjects' but also on the maternal genotype. Genetically *fmr-1*$^{+/0}$(WT) males born to *fmr-1*$^{+/-}$ (H) females (H>WT), similarly to KO male offspring born to *fmr-1-/-* (KO) mothers (KO>KO), exhibit locomotor hyperactivity. The H>WT mice also have altered D2 autoreceptor function, indicating a possible diminished feedback inhibition of dopamine (DA) release. The GABAergic system also regulates DA release, in part via presynaptic $GABA_B$ receptors located on midbrain dopaminergic neurons and GABAergic interneurons. Using baclofen, a $GABA_B$ receptor agonist, we performed an initial assessment of the GABAergic system and its role in modulating locomotor activity. We found that the behavioral dose response of KO>KO compared to WT>WT mice is shifted leftward, indicating an enhanced sensitivity to the locomotor-reducing effects of baclofen. A follow-up experiment revealed that all progeny of mutant mothers (H>WT, H>KO, and KO>KO) showed enhanced responsiveness to baclofen. This suggests that the $GABA_B$ system is altered by the maternal genotype. Regardless of whether this maternal effect occurs in the prenatal environment, during postnatal maternal care, or both, it produces a long-term neurochemical and behavioral change in the offspring lasting to adulthood.

27. NEUROBIOLOGICAL CORRELATES OF DEPRESSIVE SYMPTOMOLOGY: AN EXPLORATION OF SEX-DEPENDENT ALTERATIONS IN MOTIVATION, ANHEDONIA, AND COPING STRATEGIES. Crockett, A[1].; Fleming, D[1].; Tu, K[1].; Sirkin, M[2].; Bardi, M[2]; Kinsley, C.H[2]; [1]Lambert, K.G. [1]Dept of Psychology, Randolph-Macon College, Ashland VA 23005; [2] Dept of Psychology, University of Richmond, VA 23233 Responsiveness to various forms of stressors may regulate the intensity of depressive symptoms. Specifically, effective coping strategies may reduce the toxic effects of chronic stress, subsequently building resilience against the onset of depression. Previously our lab demonstrated that male rats profiled as active, passive, or flexible copers at weaning continued to exhibit varying stress response profiles through adulthood. In general, flexible copers exhibited more adaptive behavioral and neurobiological responses to both acute and chronic stress (Lambert et al., 2006). Due to reported sex differences in depression rates in humans, the current study investigated behavioral, endocrinological, and fos-immunoreactive responses in both male and female passive, active, and flexible copers. In accordance with human observations, females showed more vulnerability to stress-induced depression symptomology by consuming less sucrose solution during a chronic stress paradigm than males ($p=.04$) although females consumed more sucrose during the baseline observations ($p=.01$). Further, fecal corticosteroid levels were higher in females during the second week of chronic unpredictable stress ($p=.02$). Focusing on coping strategies, flexible copers demonstrated more efficient grooming in a fur-challenge test ($p=.01$) and an interaction between sex and coping strategy was observed in the conditioned fear test ($p=.03$) with the passive females exhibiting more defensive behavior than passive males. In the first of three swim tasks, flexible females exhibited longer floating durations than flexible males ($p=.03$); over the course of three swim tests, however, all animals increased float durations. No effects were observed in fos-immunoreactivity in nucleus accumbens or lateral septum upon the re-introduction of sucrose. Overall, the current study demonstrates several sex differences in stress responsivity that may explain sex-dependent differences in vulnerability to depression symptoms.

Human Studies

28. TRAINING-INDUCED FUNCTIONAL ACTIVATION CHANGES IN SCIENTIFIC HYPOTHESIS GENERATION: AN FMRI STUDY Kwon, Y. J.1; Choi, Y. H. 1; Lee, J. K.1; Lee, H. N. 2 1Korea National University of Education, Chungbuk 363-791, Korea; 2Kyungpook National University, Daegu 702-701, Korea. Although training-induced changes in brain activity have been previously examined, plasticity associated with complex learning (e. g. scientific hypothesis generation) remains understudied. The aim of the present study was to investigate the learning-related changes in brain activation that were induced by the training of hypothesis generation skills about biological phenomena. Eighteen high school student participants were scanned twice with functional magnetic resonance imaging (fMRI) before and after training during a four-month interval. The experimental group was trained through thirteen biological hypothesis generation programs (participants creating hypothesis by themselves), but the control group was given only hypothesis understanding program (participants understanding hypothesis by teacher's explanation) during the four-month period. The results have shown that the left prefrontal cortex, occipito-parietal route were activated during hypothesis generation in both groups. In addition, the brain activation of the trained group was increased in the left medial frontal gyrus which was related to working memory load and higher-order inferential processes. However, the activation after training was decreased in the left postcentral gyrus which was associated with the perception processes of visual information or task difficulty. In control group, there are no significant changes in their brain activity. Furthermore, the results have suggested that the medial frontal gyrus region is the critical area for training of hypothesis generation skills.

29. NEURAL CORRELATES OF CLASSIFICATION ABILITY AS REVEALED BY FMRI OF CLASSIFYING LIVING ORGANISMS Lee, I. S.; Lee, J. K.; Kwon, Y. J.; Yang, I. H. 1Korea National University of Education, Chungbuk 363-791, Korea Classification ability is a kind of the inductive inference, and it has been regarded as one of core reasoning processes in scientific inquiry. It is an important ability to the way of recognizes well-ordered systems from the nature¡¯s complexity and diversity. How does people classifying in the real-world? What does happen to their brain? It is still unclear that the neuro-cognitive perspective of classification ability. We hypothesized that classification ability would activate specific regions of frontal or parietal cortex that were common to those of previous inductive reasoning tasks. We report here a novel block designed fMRI study employed to investigate the neural correlate of classification ability associated with undertaking classification tasks. Eighteen healthy right-handed adult (male 9, female 9) subjects participated to this study. Classification task was consisting of nine different pictures of the animal, plant, and microorganism. We scanned brain activity during classifying the organisms in the stimuli by their own criteria. Also, they were performed classification paper task. Through the analyzing, we calculate the classification ability quotient (CQ; Kwon et al, 2007). The results have shown that the bilateral cerebellum, cuneus, left middle and medial frontal gyrus, inferior occipital gyrus, right lingual gyrus, middle occipital gyrus, and superior parietal lobule (SPL) were activated during classifying living things. Especially, the right superior parietal lobule was strongly correlates with behavioral results (CQ). This area has been previously associated with visual working memory load. A high-order analysis covarying participants' CQ score measures found correlations with individual BOLD activation strength in right SPL (BA 7, $P < 0.000$, $r = 0.75$). In addition, this result can be proposed as a alternative form of the development of instrument for measuring classification ability based on the brain imaging technique instead of paper test.

30. BRAIN-BASED DIFFERENCES BETWEEN CREATING AND UNDERSTANDING CAUSAL KNOWLEDGE Lee, J. K.1; Lee, I. S.1; Kwon, Y. J.1; Kang, M. J2. 1Korea National University of Education, Chungbuk 363-791, Korea; 2Dongyang University, Gyeongbuk 750-711, Korea. An understanding of relations between causes and effects is essential for making sense of the dynamic physical world. Also it is very important to make a scientific explanation. However, it has been argued that this understanding of causality depends on both perceptual (only passive understanding) and inferential (creating knowledge by themselves) components. Therefore, to investigate whether creating and understanding causal knowledge rely on common or distinct processes, we investigated fifteen healthy male subjects' brain activation using 3.0 Tesla fMRI. The data were statistically analyzed using SPM2 software. The results had shown that the creating causal knowledge process was found to have independent brain network and it was different from the brain network of the understanding causal knowledge process. Although the same causality of creating or understanding was administered to participants, the creating strategy was shown a prominent activation in the left prefrontal cortex area and the understanding strategy was the right prefrontal cortex area. Significant activation difference between creating and understanding causal knowledge were found bilaterally in the middle frontal gyrus, and superior temporal gyrus; the left lateralized in the putamen and inferior parietal lobule. The result of this study shows that the direct understanding of causality and the ability to create causality depend on different hemispheres of the divided brain. This finding implies that the creating and understanding causal knowledge is not a unitary process and that creating and understanding causal knowledge can proceed independently.

31. OLFACTORY TESTING FOR EARLY DIAGNOSE OF ALZHEIMER´S DISEASE. Guevara-Guzmán, R.; Aburto-Arciniega M and *Severiano, P. Departamento de Fisiología, Facultad de Medicina; *Facultad de Química. Universidad Nacional Autónoma de México, 04510 México, D.F. México. Alzheimer's disease is the most common cause of dementia in the elderly. One of the histopathological characteristics of this disease is the formation of senile plaques whose protein component is the peptide beta amyloidal. There is little information regarding research work with an epidemiological focus on the olfactory disorders in population with high risk of showing cognitive alterations, common characteristics of diseases such as Alzheimer and Parkinson. Our laboratory designed a questionnaire on odor recognition. 1000 questionnaires were applied to our national population. We chose a population ranging from 18 to 94 years old from different parts of Mexico. The results showed that there were no significant differences in odor recognition between the young and the elderly populations. The odors the population identified in 98% were lime, rose, pineapple, banana, onion, gasoline, chocolate, cinnamon, peach and orange; these results agree with those of odor testing performed by other researchers such as Dotty and cols, 1984. We found out that when 10 among all odors were applied to a population with clinic diagnostic of mild AD, they showed a 50% decrease in detection and identification of odors (olfactory threshold). In another elderly population without cognitive deterioration, we found out that odors such as pineapple, lime, apple, garlic and coffee needed to increase the concentrations in 5 logarithmic units, compared with the young population. In the case of discriminating olfactory tests, it was noticeable that young population's threshold to garlic was higher than that of the elderly; whereas their threshold to coffee was lower. We believe that the odor test may be an aid in the early diagnose test to detect changes in the olfactory threshold before the cognitive alterations show up. Grants: SDEI PTID.05.5.IN216905 and 24784M.

32. REM SLEEP-RELATED MOOD REGULATION IN PATIENTS WITH PARKINSON'S DISEASE. [1,2]McNamara, P.; [1]Auerbach, S.; [1,2]Harris, E.; [1,2]Durso, R. [1]Boston University School of Medicine and [2]Boston VA Medical Center, Boston, MA 02130 USA. REM Behavior Disorder and mood dysfunction is common in patients with Parkinson's disease (PD). The aim of this study was to assess potential behavioral links between EEG indices of REM and daytime indices of mood functions in patients with PD. Twenty male patients with mid-stage (H-Y Stage II and III) Parkinson's disease underwent overnight polysomnography and then given tests of mood function and emotional memory retrieval the next day. Bonferroni-corrected Pearson product moment correlations were computed for measures of sleep architecture and daytime mood and cognitive performance. Mood was assessed with the 'positive and negative affect' scales or PANAS, a 20-item checklist of emotion words that the respondent uses to indicate mood in the last week, and with an emotional memory retrieval task (individual PANAS items were provided as cue-words to retrieve emotional memories one hour after the PANAS itself was administered). REM percentage (of total sleep) correlated significantly ($p>.001$) with negative measures of daytime mood including the mean difference score for latency to retrieval for emotion vs. neutral words as well as the following items on the PANAS scales: 'distress' ($r=.60$); 'upset' ($r=.56$); 'irritable' ($r=.31$); 'nervous'($r=.59$); and 'jittery' ($r=.54$). Overall correlation of REM% with total PANAS score was .44 ($p<.001$). Stage II sleep was not significantly correlated with any of the PANAS items or PANAS total. REM sleep durations may exhibit a correlation with daytime mood regulation in patients with PD and this correlation is not seen with Stage 2 NREM sleep. This work is supported in part by NIMH Grant No. 1R21MH076916-01A2.

33. ATTENTION, EMOTION AND LANGUAGE IN PATIENTS WITH RIGHT VERSUS LEFT-ONSET PARKINSON'S DISEASE. McNamara, P.; Harris, E.; Durso, R. Dept. of Neurology. Boston University School of Medicine and Boston VA Medical Center, Boston, MA 02130 USA. We hypothesized that Parkinson's disease (PD) patients with left-onset disease (implying right-sided neostriatal and hemispheric involvement) would evidence significantly greater impairments in attentional, emotional memory retrieval and pragmatic language functions relative to right-onset patients. Seventeen PD patients with right-onset disease and 17 age, education and severity-matched PD patients with left-onset disease were assessed with a set of neuropsychologic, emotional memory retrieval (using emotion vs. neutral words as cues to retrieve memories), and pragmatic language production tasks (producing narratives in differing social contexts). Relative to right-onset patients, left-onset patients were significantly impaired on executive control tasks (Stroop (117.7 (45.8) vs. 80.9 (33.1). $p=.004$), and for the emotional memory task: mean difference score for latency to retrieval for emotion vs. neutral words was 1.39 (34) secs for left onset and 1.0 (41) secs for right onset patients ($p=.045$). On pragmatic production tasks, left-onset patients produced significantly fewer number of words per sentence (12.4 (3.8)) than the right-onset group (21.5 (15.9), $p = .03$), fewer personal pronouns, fewer referential links (deitic terms) to context, greater mean numbers of negative emotion words (left-onset mean per sample: 0.80 (.48)) vs. right-onset mean per sample: (.42 (.34)), $p=.01$), and greater mean numbers of fillers (2.4 (2.1) vs. (.04 (.06), $p=.01$). Executive control, emotional memory retrieval latencies and selected pragmatic language skills are significantly impaired in PD patients with left-onset disease relative to control patients with right-onset disease. This work is supported in part by NIDCD Grant no. 1R01DC007956-01A2.

34. NEUROACTIVE STEROIDS AND SELF-REPORTED PAIN IN VETERANS WHO SERVED DURING OPERATION ENDURING FREEDOM / OPERATION IRAQI FREEDOM. Kilts, J.D.; Calnaido, R.P.; Payne, V.M.; Calhoun, P.S.; Tupler, L.A.; Naylor, J.C.; Hamer, R.A.; Morey, R.A.; Beckham, J.C.; Strauss, J.L.; Massing, M.W.; Shampine, L.J.; Connor, K.M.; Davidson, J.R.T.; Marx, C.E. Depts. of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC; Durham Veterans Affairs Medical Center; Dept. of Psychiatry, University of North Carolina, Chapel Hill, NC. A number of investigations report analgesic and anxiolytic effects of neuroactive steroids (NS) in animal models, but few studies have examined the relationship between pain and NS in clinical populations. Based upon the analgesic actions observed for multiple NS in animals, we hypothesized that levels of endogenous NS are negatively correlated with pain perception in humans. Recent data demonstrate that nearly half of Operation Enduring Freedom / Operation Iraqi Freedom (OEF/OIF) veterans report continued pain post-deployment. We thus interviewed 90 male veterans who served during OEF/OIF to assess four measures of self-reported pain, and determined their serum NS levels by gas chromatography / mass spectrometry (allopregnanolone, pregnenolone) or radioimmunoassay (dehydroepiandrosterone [DHEA], DHEA sulfate [DHEAS], progesterone). Stepwise regression analyses were conducted to investigate the relationship between psychiatric assessments and NS, including smoking, alcohol use, age, and history of traumatic brain injury (TBI) as covariates. Allopregnanolone levels are inversely associated with chest pain ($p=0.013$) and low back pain ($p=0.044$), and DHEA levels are inversely associated with muscle soreness ($p=0.024$). DHEAS levels are positively associated with chest pain ($p=0.001$). Additionally, there is a positive association between history of TBI and muscle soreness ($p=0.002$). NS may be relevant to the pathophysiology of pain perception in this veteran cohort and represent a future treatment strategy for pain disorders.

35. GENDER DIFFERENCES DURING THE PERCEPTION OF SUFFERING EXPERIENCE: A FMRI STUDY. Barrios F.A.; Mercadillo R.E.; Díaz J.L.; Salgado P.M. Instituto de Neurobiología, UNAM, Queretaro QRO, México. Gender differences are reported in neurocognitive processes related to emotional experiences and moral reasoning [1]. Compassion belongs to a category of emotions related to moral judge, and it is elicited by the perception of suffering in other and motivates action to help the suffering[2]. In this study we identified the existence of gender behavioral differences related to compassion and their nenurobiological substrate. Sixteen right handed volunteers (8 women and 8 men, 28 ± 3 years old) participated in this study after informed written consent. SCL-90 and ITC tests were applied to identify mental disorders and estimate temperament. Functional MR images were acquired using a 3.0 T G.E. scanner, using a BOLD-EPI-GRE. A series of 100 validated pictures [3] selected from IAPS were projected as an event-related paradigm. 14 compassionate pictures were presented among 76 social neutral pictures. All images were analyzed using SPM. Men showed activation in the left prefrontal cortex only, while women manifested activation in subcortical areas related to emotional experience (parahippocampal gyrus, insular cortex, anterior and posterior cingulated cortices), aversive memory, cognitive control, and decision making (temporal pole, prefrontal and orbitofrontal areas). Cortical areas are related to cognitive processes in moral judgments, semantic concepts and attribution of intentionality. Subcortical activation presented in women may imply social skills required to response of offspring needs and differential cultural expectations. References [1] Singer T et al. (2006). Nature, 439, 466-469 ; [2] Haidt J (2003). The moral emotions. In Davidson RJ et al. Handbook of affective sciences. Oxford University Press; [3] Mercadillo RE et al. (2007). Percept Mot Skills, 105, 661-676.

36. HUMAN BEHAVIORAL PATTERN MONITOR EXEMPLIFIES DIFFERENCES BETWEEN ACUTE BIPOLAR DISORDER MANIA AND SCHIZOPHRENIA SUBJECTS Authors: Kincaid MJ, Minassian A, Ferguson EJ, Young JW, Geyer MA, Paulus MP, & Perry W Department of Psychiatry, University of California, San Diego Background: During acute psychotic episodes, similar behaviors are commonly observed in bipolar disorder (BD) and schizophrenia (SCZ) patients, making differential diagnosis difficult. We recently developed the human Behavioral Pattern Monitor (hBPM), based on the rodent open field, and used it in this study to examine exploratory behavior of acutely ill BD and SCZ patients. Methods: 14 Psychotic BD, 16 SCZ, and 22 non-patient comparison (NC) subjects were led into a minimally furnished room with 11 different toys and no chairs. Each subject was instructed to wait alone while other parts of the experiment were set up. Behavior was recorded for 15 minutes with a video camera inconspicuously embedded in the ceiling. Videos were scored frame by frame for exploratory behavior, i.e., number of object interactions, repeated interactions (perseveration) with like objects, and time spent walking.Results: BD subjects exhibited greater object interactions ($t=5.6, p<0.0001$), perseveration ($t=6.1, p<0.0001$), and walking ($t=4.4, p<0.0001$) compared to NC subjects, and more object interactions ($t=5.8, p<0.0001$), and perseveration ($t=2.8, p<0.001$) compared to SCZ subjects. Conclusion: The assessment of exploration in the hBPM offers an opportunity to differentiate between two neuropsychiatric patient groups that exhibit similar behaviors during periods of high acuity. Used in conjunction with other quantitative measures of exploration (e.g., locomotor patterns), the hBPM may prove a useful tool for differentiating BD and SCZ patients in an acute setting.

Motivation and Social Behavior

37. ANABOLIC STEROID MODULATION OF NEUROPEPTIDE Y LEVELS IN BRAIN REGIONS CONTROLLING ANXIETY AND REPRODUCTIVE BEHAVIORS IN PUBERTALS RATS. 1Santiago-Gascot ME, 2Santiago S, 1Barreto-Estrada JL. 1School of Medicine, Department of Anatomy and Neurobiology, Medical Sciences Campus, 2Department of Biology, University of Puerto Rico, San Juan, PR 00936. Anabolic androgenic steroids (AAS) are synthetic derivates of testosterone used to treat a variety of medical conditions. Lately, the abuse of AAS has been leading to a diverse spectrum of secondary effects including physiological and behavioral changes. There is a strong relationship between AAS and behavior. Besides AAS modulation of behavior, synthetic androgens can regulate neuropeptides. Similarly, neuropeptides have been shown to modulate different domains of behavior. Neuropeptide Y (NPY) is one of the most abundant neuropeptide in the CNS, and has been shown to be expressed in neuronal circuits involved in anxiety, reproductive behaviors and energy homeostasis. Therefore, we aimed to assess the cellular mechanisms by which neuropeptides mediate the maturation of endocrine neural networks across critical developmental periods (puberty). Females and males were under continuous systematic high dose exposure (7.5 mg/kg) of 17α-methyltestosterone (17α-meT) for two weeks. Thereafter, we performed brain punches at the medial preoptic area (mPOA), ventromedial nucleus (VMN) and amygdala regions (AMY) to measure neuropeptide Y (NPY) levels by radioimmunoassay. In females, we observed a significant decrease in NPY levels in the AMY, while in males a significant increase in the VMN was observed. Our experiments suggest that AAS modulate neuropeptides in brain centers controlling behavior and that NPY might be involved in anxiety and reproductive behaviors after AAS exposure. MBRS-RISE (GM61838), RCMI (G12RR03051), NIH-NCRR (P20RR016470).

38. ANABOLIC STEROIDS AFFECT EMOTIONAL MEMORY IN FEMALE PUBERTAL RATS: POSSIBLE ROLE OF NPY [1]Ramos-Pratts KM, [1]Santiago-Gascot ME, [2]Villafane B, [1]Pérez-Acevedo NL, [1]Barreto-Estrada JL. [1]School of Medicine, Department of Anatomy and Neurobiology, Medical Sciences Campus, [1]Department of Biology, Rio Piedras Campus, University of Puerto Rico 00936 The amygdala (AMY) is a key forebrain structure controlling emotional states that has been shown to express neuropeptide Y (NPY); an important neuromodulator in the mammalian brain. NPY has been associated with regulation of physiological processes such as energy homeostasis, cognitive processes and anxiety. Previous studies had demonstrated that all these behaviors can be affected after misuse of anabolic androgenic steroids (AAS). AAS are derivates of testosterone and their abuse have been increasing at an alarming rate, especially among adolescents. Therefore, we aimed to assess NPY modulation in the AMY after chronic exposure to AAS in pubertal rats. Animals were under continuous systematic high dose (7.5 mg/kg) of 17α-methyltestosterone for two weeks. Anxiety was assessed using the Elevated Plus Maze (EPM) and risk assessment behaviors (RABs). In addition, emotional memory was measured using the Passive Avoidance Task (PAT). All the behaviors were done while animals were still under drug exposure. Food intake and body weight were also monitored. Micropunches were then taken from the AMY to determine NPY levels using RIA. Results showed that NPY levels were increased in females AMY, while males were not affected. No differences were found in the EPM or RABs. Although no differences were found in the PAT in males, there was a tendency to impair emotional memory in AAS-treated females. These females increased body weight and food intake after AAS exposure. Taken together, our results suggest that AAS can modulate emotional memory and energy metabolism in adolescent females, possibly through NPY-related neural circuits. MBRS-RISE (GM61838), RCMI (G12RR030551), NCRR-NIH (P20RR016470).

39. ANABOLIC STEROIDS AFFECT SEXUAL MOTIVATION IN MALE PUBERTAL RAT: POSIBLE ROLE OF NPY 1Parilla-Carrero J, 2Santigo-Gascot ME, 1Roig-López , JL, 2Barreto-Estrada JL, 1Department of Science and Technology, Universidad del Este, Carolina, PR 00984, 2Department of Anatomy and Neurobiology, Medical Sciences Campus, University of Puerto Rico, San Juan, PR 00936 Previous experiments have demonstrated the role of the ventromedial nuclei (VMN) of the hypothalamus in motivational components of sexual behavior. Our group of investigators has shown an increase in NPY levels in the VMN after exposure to anabolic androgenic steroid (AAS) in male pubertal rats, while the mPOA was not affected. The aim of this study was to determine if pubertal male rats exposed during puberty (PN33) to 17 alpha-methyltestorene displayed changes in sexual motivation when paired with a receptive female. Motivational and copulatory parameters were analyzed four weeks after AAS withdrawal and when animals were in the adult stage. AAS-treated rats showed a tendency to decrease the latency to the first mount as well as a decrease in the time from the first mount to the first ejaculation. Similarly, when compared to controls, the latency to the first ejaculation was significantly decreased in AAS exposed animals, and an increase in multiple ejaculations was observed. On the other hand, anogenital investigations, frequency of mounts and copulatory performance were not affected. This study shows that androgen exposure have long term effects when administered during puberty and suggests that NPY might be an important substrate being modulated by AAS to affect sexual motivation. In order to explore which kind of molecular mechanism, we plan to use semi-quantitative Real-time PCR to look for NPY messengers and receptors at the sexually associated nuclei. MBRS-RISE (GM61838), RCMI (G12RR030551), NCRR-NIH (P20RR016470).

40. ANXIETY, SOCIAL, AND SEXUAL BEHAVIOUR AND NEUROENDOCRINE MEASURES IN ADULT RATS PERINATALLY EXPOSED TO CALORIE RESTRICTION. Kent, S., Levay, E.A., Govic, A., Hazi, A., Penman, J., Paolini, A.G. Sch Psychological Science, La Trobe University, Melbourne, Australia. Environmental stimuli such as caloric availability during the perinatal period exert a profound influence on the development of an organism. Studies in this domain have focused on the effects of under- and malnutrition while the effects of more mild levels of restriction have not been delineated. Rat dams and their offspring were subjected to one of five dietary regimens: control, CR50% for three days preconception, CR25% during gestation, CR25% during lactation, and CR25% during gestation, lactation, and post-weaning (lifelong). Adult male offspring were tested in three tests of anxiety: the elevated plus maze, open field test, and emergence test, as well as the social interaction and sexual behaviour tests. Offspring from the preconception group exhibited greater anxiety-like behaviour in all three tests. Gestation and lifelong CR offspring exhibited more social interaction with conspecifics; the lifelong group exhibited greater dominant type behaviours. Preconception and lactation CR resulted in offspring that displayed an enhanced and more efficient copulatory pattern. Basal serum ACTH was reduced by 35-43% in all dietary regimens except the lifelong group. Although a similar trend was observed for corticosterone concentrations, only the decrease in the lactation group was significant. Testosterone was enhanced by preconception and lifelong CR and leptin levels were enhanced by 37% in the preconception group. Plasma adrenalin was reduced by 33-49% as a result of all dietary regimens and noradrenalin was reduced in the gestation and lifelong groups by 51% and 39%, respectively.

41. EFFECTS OF 5-HT1B AND 5-HT 2C RECEPTOR AGONISTS ON BEHAVIORAL SATIETY SEQUENCE IN RATS. Mancilla-Díaz, J.M; López-Alonso, V.E; Escartín-Pérez, R.E; Rito-Domingo, M. Psychobiology of the Eating Laboratory, FES-Iztacala, Universidad Nacional Autonoma de Mexico. Previous studies have shown that feeding behavior is affected by serotonergic neurotransmission, mainly in the hypothalamus. The serotonergic system plays a significant role in the control of feeding behavior mainly controlling carbohydrate intake. Furthermore, it has been reported that 5-HT1 and 5-HT2 serotonin receptors are required for regulating serotonin activity in the control of food intake. However, the effect of this regulatory activity on particular behavioral mechanisms remains unclear. The aim of the present study was to evaluate the effects of CP93129 (5-HT1B receptor agonist) and Ro-60-0175 (5-HT2C receptor agonist), injected into the paraventricular nucleus (PVN) on the behavioral satiety sequence (BSS) in rats. Male Wistar rats were individually housed in clear Perspex cages with free access to individual sources of protein, carbohydrate, fat and water. The experimental room was maintained at 21± 1 ˚C on reversed light-dark cycle (light on at 21.00 h). The behavioral test consisted in the analysis of the duration of three mutually exclusive behavioral categories within 60 min (feeding, resting, and activity) at the beginning of the dark phase; food intake was measured in the same observation period. The results suggest that the agonist 5-HT1B and 5-HT2C into the paraventricular nucleus induce hypophagia. The co-administration of 5-HT1B and 5-HT2C receptor agonists produced stronger hypophagic effects than the administration of each agonist alone. The analysis of the BSS revealed that the co-administration of drugs CP 93129 + Ro-60-0175 induces the early development of the satiety sequence, preserving the typical pattern of the BSS. These findings suggest that the specific 5-HT receptor agonist activation affected serotonergic modulation of feeding behavior in a functionally selective way. Sponsored by PAPIIT IN304406 and IN309008.

42. CENTRAL LEPTIN OR POMC OVEREXPRESSION PARTIALLY RESTORES DECREASED VOLUNTARY WHEEL RUNNING WITH AGE. Scarpace, P.J; Tümer, N. Department of Pharmacology and Therapeutics, University of Florida, Gainesville, FL 32610 and Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Gainesville, FL 32608. Physical activity levels diminish with age, and voluntary wheel running (WR) is one form of physical exercise. We examined the impact of central overexpression of leptin and pro-opiomelanocortin (POMC) on the extent of voluntary wheel running. Leptin was overexpressed in hypothalamus and POMC in both hypothalamus and nucleus of the solitary tract (NTS) by rAAV-mediated gene delivery. Both leptin and POMC increased sympathetic nervous system activity evidenced by elevated brown fat uncoupling protein expression and elevated tyrosine hydroxylase and dopamine beta-hydroxylase expressions in the adrenal grand. There was a substantial impact of age on WR with decreases in WR beginning at 6 months (mo) compared with 3 mo and 7-fold and 8-fold decreases, respectively by 16 and 30 mo. In 6 mo-old, hypothalamic leptin overexpression increased WR greater than two-fold compared with control vector or pair-fed control vector, while central leptin infusion increased WR by two-fold in 16 mo old. Hypothalamic and NTS POMC overexpression in 30 month old rats also increased WR by two-fold. These data indicate that age decreases WR, whereas leptin or POMC activation partially restores WR activity. The underlying mechanism may involve increased sympathetic nervous system activity. Supported by VA Medical Research and NIH AG-26159, P30 AG028740.

43. IONIC MECHANISMS OF GHRELIN-INDUCED DEPOLARIZATION ON PEDUNCULOPONTINE TEGMENTAL NEURONS IN RATS: AN IN VITRO STUDY. Sasaki, K.; Kim, J.; Nakajima, K.; Wayner, M.J.[1]; Oomura, Y.[2] Div. of Bio-Information Eng., Univ. of Toyama, Toyama, Japan; [1]Dept. of Biol., Univ. of Texas at San Antonio, Texas, USA; .[2]Dept. of Physiol., Kyushu Univ., Fukuoka, Japan. Ghrelin is produced in some peripheral organs and brain, and stimulates growth hormone (GH) secretion and food intake via GH secretagogue receptors (GHS-Rs). Recent studies further indicate that ghrelin is involved in the regulation of sleep-wakefulness. Pedunculopontine tegmental nucleus (PPT), one of the brain sites that regulate sleep-wakefulness, also expresses GHS-Rs. However, the effects of ghrelin on PPT neurons remain unclear. Hence, we investigated the effects of ghrelin on PPT neurons using brain slice preparations and the whole-cell patch clamp recording technique. Bath-application of ghrelin depolarized PPT neurons, and the depolarization persisted in the presence of tetrodotoxin. The ghrelin-induced depolarization was significantly decreased, but did not disappear by either an increase of extracellular K^+ concentration from 4.25 to 13.25 mM or a replacement of extracellular Na^+ with N-methyl-D-glucamine (NMDG). However, it was completely blocked by both an increase of extracellular K^+ and the replacement of extracellular Na^+ with NMDG. An inhibitor of the Na^+ and Ca^{2+} exchanger did not have any effect on the depolarization. These results suggest that the ghrelin-induced depolarization is mediated by two ionic mechanisms; that is, a decrease of K^+ conductance and an increase of nonselective cation conductances, and that ghrelin participates in the regulation of sleep-wakefulness via an excitatory action on PPT neurons.

44. EFFECTS OF 2E-HEXENAL ON FOOD INTAKE AND ON BRAIN SEROTONIN METABOLISM IN RESTRAINED RATS. Sasaki, K.; Mochizuki, T.; Kim, J.; Nakajima, K.; Shimizu, N.[1]; Oomura, Y.[2] Div. of Bio-Information Eng., Univ. of Toyama, Toyama, Japan; [1]Dept. of Chem. & Chem. Eng., Kanazawa Univ., Ishikawa, Japan; .[2]Dept. of Physiol., Kyushu Univ., Fukuoka, Japan. 2E-hexenal is one of substances that constitute fragrance emanating from green leaves. In the present study, we examined effects of 2E-hexenal on food intake and on brain serotonin metabolism in restrained rats. On food intake, immobilization stress for 200 min before light off inhibited food intakes for 3 h from 18:00 (light off) to 21:00 and for 9 h from 18:00 to 06:00 (light on). Inhalation of 2E-hexenal (0.03%) during immobilization stress restored the decrease of 3 h food intake. For a measurement of serotonin metabolism, perfusates were obtained from the lateral hypothalamic area (LHA) by microdialysis method for 600 min. Immobilization stress was applied for 200 min after control perfusates were obtained for 200 min. Levels of serotonin and its metabolite, 5-hydrooxyindoleacetic acid (5-HIAA), in the perfusates were measured by HPLC method. Level of serotonin was increased transiently during immobilization stress, whereas that of 5-HIAA was increased gradually during and after immobilization stress. Inhalation of 0.03% of 2E-hexenal during immobilization stress blocked the increases in serotonin and 5-HIAA levels. In previous studies, we demonstrated that immobilization stress increases the level of serotonin in the LHA, and thereby inhibits food intake. Thus, present results suggest that 2E-hexenal ameliorates the inhibition of food intake by suppressing the increase of serotonin level in the LHA induced by immobilization stress.

45. STRIATAL CHOLINERGIC CONTROL OF ANTICIPATORY AND CONSUMMATORY FEEDING BEHAVIORS Michelle L Perry1 and Brian A Baldo2 Molecular and Cellular Pharmacology1 and Department of Psychiatry2, University of Wisconsin-Madison The nucleus accumbens is an important brain region involved in addiction and feeding. Feeding is a complex behavior that is composed of two phases, the anticipatory/preparatory phase in which the animal is guided by internal representations and expectations of the goal, and the consummatory phase, in which stereotyped feeding patterns are influenced by sensory taste cues. Intra-accumbens infusion of the muscarinic antagonist, scopolamine, appears to enhance appetitive/preparatory behaviors elicited by food expectation (i.e., feeding bout initiation, hyperactivity while waiting for food behind a removable barrier), while decreasing but not eliminating consummatory feeding behavior. These results indicate that muscarinic blockade does not decrease the animal's motivation to obtain food, but reduces food consumption once eating has begun. One possible mechanism that could account for these results is in the ability to switch out of a heightened state of motivational arousal and anticipation, reducing the ability of rewarding sensory taste cues to guide behavior and keep the animal focused on feeding. Cholinergic manipulations of the striatum may thus represent an interesting novel target for controlling food consumption while leaving motivation to eat unaffected, and not producing an outright negative motivational state or anorexia.

46. PREFRONTAL CORTEX AND FEEDING: ROLES OF GLUTAMATE AND MONOAMINE SYSTEMS ON FOOD INTAKE AND FEEDING MICROSTRUCTURE. Mena, J.D.; Baldo, B.A. Department of Psychiatry and Neuroscience Training Program. University of Wisconsin-Madison, Madison, WI 53719 USA. We have shown that temporary inactivation of prefrontal cortex shifts feeding behavior towards longer eating bouts with lower interspersed exploratory activity. The goal of the present study was to examine the pharmacological specificity of this effect. Glutamate and monoamine neurotransmitter systems were tested within the medial prefrontal cortex (mPFC) through the administration of selective receptor-subtype antagonists. First, intra-mPFC infusions of the AMPA receptor antagonist, CNQX, and of the NMDA receptor antagonist, AP-5, were performed under two distinct motivational conditions: food restricted rats given access to standard chow and non-food restricted rats given access to chocolate Ensure. CNQX dose-dependently increased mean feeding bout duration and decreased locomotion and rearing, while AP-5 had no effect on any measured parameter. Next, we tested the dopamine, norepinephrine, and serotonin systems using the D1 antagonist SCH 23390, the D2 antagonist Raclopride, the α1 noradrenergic antagonist Prazosin, a â1 and â2 noradrenergic antagonist cocktail consisting of ICI 118,551 and Betaxolol, the 5HT1A receptor antagonist WAY 100635, and the 5HT2A receptor antagonist MDL 11,939. Of all drugs tested, only MDL 11,939 and Raclopride elevated food intake. Other drugs had no effect on feeding-associated behaviors. It is noteworthy that combined D2 and 5HT2 antagonism represents a common mode of action of atypical antipsychotics, which are well known to have a strong weight-gain liability. Moreover, because we found that MDL 11,939 increases food intake by prolonging the overall duration of feeding, this effect may represent a novel extra-hypothalamic site for serotonergic control of satiety. Supported by: NIH Grant MH74723 (B.A.B.)

47. SEXUAL PREFERENCE IN MALE RATS PRENATALLY TREATED WITH ATD. Ferreira-Nuño, A; Olayo-Lortia, J; Fernández-Soto, C; Reyes-Gordillo, J; Olivares-Arreola, J; Velázquez-Moctezuma, J. and Morales-Otal, A. Universidad Autónoma Metropolitana-Iztapalapa. Dept. of Neuroscience. México, D. F. 09340. otal@xanum.uam.mx. Prenatal treatment of male rats with the aromatase inhibitor 1, 4, 6 androstantrien 3, 17 dione (ATD) generate the expression of bisexual behaviors during adulthood. However, these results have been a matter of controversy, because the lordosis behavior displayed by the ATD males appears when they are forced to receive mounts by a male in a closed arena. To further analyze this phenomenon, we designed a set up to assess spontaneous Sexual Partner Preference (SPP). Six acrylic cylinders were placed in an ellipse fashion, with the following stimuli tethered animals in each compartment: a sexually active male (SAM), a castrated male (CAS), a sexually receptive female (SRF), an ovariectomized female and two empty cylinders located in the poles of the ellipse. All the cylinders had a hole at the bottom. An experimental male is left in the center and is allowed to choose spontaneously in which of the six compartments enters. Experimental males were prenatally treated with A: 5 mg/day of ATD dissolved in 0.1 ml of propylene glycol (PG). B: 0.1 ml/day of PG and C : a control intact group. At 3 months of age, males were tested for the SPP. Test consists in placing the experimental male in the center during 1 minute, recording the selected cylinder. Tests were repeated 12 times and preference was determined. The control untreated group significantly prefers to enter where the SRF was located. The ATD group had a similar percentage of entrances in the cylinders where the SRF, CAS and SAM stimuli rats were located. Then in the SPP arena the ATD males didn’t show a clear bisexual partner preference.

48. EVALUATION OF PARTNER PREFERENCE IN A 3-CHAMBER TEST BOX USING HORMONE-PRIMED OVARIECTOMIZED LONG EVANS RATS D. Deecher, C. Maddage, J. Bray, S. Cosmi, A. Pawlyk & P. Alfinito Wyeth Research, Collegeville, PA 19426. Studies have reported that hormone-primed ovariectomized (OVX) rats, when given a choice of a sexually-experienced intact male (IM) or a castrated male (CM), will spend more time with the IM. This concept, commonly referred to as partner preference (PP), was further explored using a custom designed 3-chamber test box. The assays were performed under dim red light using either contact or noncontact methods. The contact method used a test box that permitted free access of the OVX rat to either the IM or CM, whereas the noncontact method prevented any physical interactions. Inexperienced male and female rats received one 40-minute sexual training session and remained paired for experimental testing. In both training and test sessions, OVX rats were hormone-primed 48 h prior to testing with estradiol benzoate (10 ug/rat) and 5 h prior to testing with progesterone (500 ug/rat). Using a video tracking system, time spent with the IM or CM was quantified to determine location preference. Partner preference was calculated as the time spent with the IM divided by the total time spent with both males. One-sample T-tests were performed for each treatment group to determine PP from no preference (score = 0.5). In the contact method, no statistically significant PP was observed in any of the 3 separate groups (n=11-12/group) tested (0.46/0.51/0.60 PP score; $p>0.05$). In the noncontact method, two of the three groups (n=12/group) did show a small but significant difference (PP score 0.65/0.60; $p < 0.008/0.03$). However, the third group did not demonstrate a significant difference (PP score 0.55; $p>0.05$). Various training paradigms were evaluated with no improvement in PP score. Determinations of PP utilizing contact and noncontact choice tests were highly variable. Thus, further work need to be performed to validate PP as a measurement for drug discovery.

49. ALTERED TRAJECTORIES OF BRAIN AND BEHAVIORAL DEVELOPMENT FOLLOWING NEONATAL SEROTONIN DEPLETION *Hohmann, C.F.; *Anderson, M.E.; ^Smith-Conner, K.; ^Blue, M., *Department of Biology, Morgan State University and the ^Kennedy Krieger Institute, Baltimore MD. Previous studies in our laboratories have shown that selective neonatal depletions of the serotonin projections to the forebrain result, by adulthood, in altered cortical cytoarchitecture, neurochemistry and disruptions of social/emotional behaviors in mice. The brain and behavioral changes observed in mature mice are analogous to pathologies and behavioral criteria associated with autism spectrum disorder [ASD]. The current study aims to characterize the behavioral trajectories and maturational brain changes in such lesioned mice [5,7-DHT] in comparison with sham injected [VIC] and un-injected, age matched controls [AMC]. Balb/CByJ pups from the same litters received neonatal injections of 5,7-DHT (in saline) or saline alone into the medial forebrain bundle area on the day of birth. Males and females, from more than three different litters in each group, were either perfused for stereological assessment of cortical histology or tested on a homing task based on odor discrimination. Both 5,7-DHT and VIC mice showed a significant increase in cortical volume at PND 7 compared to AMCs. This volume change had normalized by adulthood. In contrast, only 5,7-DHT mice showed a deficit in time spent with home vs. clean bedding. When tested on clean vs. peppermint flavored bedding, all groups significantly preferred the clean bedding, indicating that the deficit is not due to a difference in olfactory perception. This suggests a social deficit in the 5,7-DHT mice as early as PND7. Supported by U54MH66417.

50. ENHANCED MATERNAL AGGRESSION IN REPRODUCTIVELY EXPERIENCED DAMS IS ASSOCIATED WITH ALTERATIONS IN CENTRAL VASOPRESSIN AND OXYTOCIN ACTIVITY. Nephew, B.; Bridges, R.S.; Byrnes, E.M. Department of Biomedical Sciences, Tufts University, Cummings School of Veterinary Medicine, North Grafton, MA 01536 USA Reproductive experience (i.e. pregnancy and lactation) leads to alterations in neural and endocrine function that persist post-weaning. We propose that one of the functional consequences of these changes may be improved care of subsequent litters. Based on this hypothesis, we recently examined the effect of reproductive experience on maternal aggression in lactating rats. Maternal aggression during early lactation is critical for the protection of altricial young. In the current study, the intensity of maternal aggression was significantly increased in multiparous females (i.e. second-time mothers) when compared to primiparous females (i.e. first-time mothers). As recent studies indicate that the central vasopressin and oxytocin systems are involved in the control of maternal aggression, we also examined mRNA expression of vasopressin, AVP V1a receptors, oxytocin and oxytocin receptors using real-time qPCR in primiparous and multiparous females. Six nuclei important for the expression of maternal aggression were examined; the paraventricular nucleus, supra-optic nucleus, central amygdala, medial amygdala, bed nucleus of the stria terminalis, and lateral septum. Reproductive experience induced changes in both the vasopressin and oxytocin systems in multiple brain regions. These results indicate that one consequence of prior reproductive experience is enhanced maternal aggression which may be mediated by changes in central vasopressin and/or oxytocin activity. Supported by NIH grants F32 HD048103 (BCN) and R37 HD19789 (EMB and RSB).

51. EFFECTS OF AN ER-ALPHA AGONIST ON SOCIAL BEHAVIOR IN GONADALLY INTACT AND GONADECTOMIZED MALE AND FEMALE MICE. Clipperton, A.E.; Almey, A.; Melichercik, A.; Choleris, E. Dept of Psychology, Univ of Guelph, Ontario, Canada. Gonadal hormones mediate affiliative and agonistic social interactions. Removal of the estrogen receptor alpha (ERα) gene reduces male aggression, but this could be due to developmental or activational effects of ERα. There has also been little or no research on the effects of ERα in female territorial aggression. We investigated the effect of gonadectomy (gonadex) and the ERα agonist PPT on behavior of male and female mice in the intruder test. We videotaped the 15 min interactions of individually housed mice with a same-sex, gonadex intruder, and then analyzed these interactions for 21 behaviors. We observed some sex differences: as expected, only the intact males attacked the intruders, but when other types of agonistic (dominance related) behaviors were included, the overall aggression of males and females was not different. Males also shifted between behaviors more frequently and were less social than females. Gonadex reversed these differences. Castration decreased behavioral shifting, and increased social behavior. Ovariectomy (ovx) increased behavioral shifting and decreased social behaviour. In both sexes, gonadex decreased sex-typical aggression (attacks in males, other dominance behaviours in females). ERα agonist PPT had few effects in gonadally intact mice, but increased sex-typical aggression in castrated and ovx mice. This suggests a role for the other ER (ERβ) in male and female aggression. We show here that an ethological analysis allowed both the study of territorial aggression also in female mice and the assessment of gonadex and the role of ERα in male and female aggression. Supported by NSERC.

52. NEURAL AND PHARMACOLOGICAL CHARACTERIZATION OF SOCIAL APPROACH INDUCED BY PLAYBACK OF 50-KHZ ULTRASONIC VOCALIZATIONS IN THE RAT. Wöhr, M.; Sadananda, M.; Schwarting, R.K.W.; Experimental and Physiological Psychology, Philipps-University of Marburg, Germany. The fact that rats emit different types of ultrasonic vocalizations in a variety of motivationally relevant contexts has received increasing experimental attention, since such calls might serve as indices of the animal's affective state. Thus, 50-kHz calls are emitted during play and tickling, indicating a positive affective state. However, little is known about the adaptive function of 50-kHz calling, though it has been suggested that 50-kHz calls could serve as social signals. To test this communicative hypothesis, responses to playback of 50-kHz calls were measured in the recipients. Playback of 22-kHz calls, which are emitted in aversive contexts, and background noise constituted the controls. Results clearly showed that playback of 50-kHz calls induces approach behavior, whereas playback of 22-kHz calls induces locomotor inhibition. Background noise was inefficient. Subsequently, neural activity in response to playback was revealed by means of c-fos immunocytochemistry. While 22-kHz calls induced c-fos expression in perirhinal cortex, amygdalar nuclei and the periaqueductal gray, 50-kHz calls elicited expression in frontal association cortex, nucleus accumbens, and the paraventricular thalamic nucleus. Finally, it was tested whether call-induced social approach can be manipulated by pharmacological agents. Animals received 1 mg/kg morphine, naloxone, or saline. Results showed that the opioid-antagonist naloxone has an inhibitory effect on social approach. In total, the results demonstrate that playback of 50-kHz calls induces social approach, which is associated with brain activity in areas implicated in reward and partly opioid-dependent. Therefore, this test gives valuable insights into the social brain and might offer a suitable approach for phenotypic description in animal models of neurodevelopmental disorders characterized by social deficits, such as autism.

53. EARLY LIFE FAMILY STRUCTURE INFLUENCES EMOTIONALITY AND SPONTANEOUS PARENTAL BEHAVIOR IN ADULT PRAIRIE VOLES. Ahern T.H.; Young L.J. Dept. of Psychiatry and Neuroscience Program, Emory University, and The Center of Behavioral Neuroscience, Atlanta, GA 30329 USA. Early life experience exerts a profound influence on neurophysiology and behavior in adulthood. Prairie voles are socially monogamous, biparental, and highly social and thus provide an ideal model for studying the effects of early social environment on development. In the wild, varying percentages of prairie vole pups are raised by single-mothers, two parents, or communal groups. We recreated this variation in the laboratory to examine the effects of biparental (BP) and single-mother (SM) care on the development of neuropeptide systems and adult behavior. These ethologically relevant groups were also compared to a typical maternal-separation paradigm (HMS180). Our first study quantified the effect of family structure on parental behavior received by pups from post-natal day 1-16. Our second analysis examined how these rearing conditions influence adult behavior, including open-field, elevated plus maze (EPM), and spontaneous parental behavior performance. The family observations revealed differences between the BP and the other rearing conditions in the percentage of time pups were alone on the nest ($F_{2,19}=16.56$, $P<0.001$), licking and grooming received ($F_{2,19}=6.67$, $P<0.01$), and when pups first venture off the nest ($F_{2,15}=8.01$, $P<0.01$). The adult offspring behavioral assays revealed a reduction in open field exploration for HMS180 males ($P<0.01$) and an increase in exploratory activity for SM offspring ($P<0.05$ for open field and EPM). Remarkably SM females showed very little spontaneous maternal behavior ($P<0.01$) in comparison to BP females. We are currently examining the effects of early life family structure on neuropeptide systems that may underlie these differences in behavior. The use of this early life paradigm in prairie voles is potentially useful for understanding how variation in early life social experience alters the neural systems underlying stress-responsiveness and adult social behaviors.

Friday, June 20, 2008

8:30-10:30 Symposium 3: Glial-neuron interactions in neuropsychiatric and neurodegenerative diseases. Chair: John P. Bruno.

ASTROCYTE-DERIVED KYNURENIC ACID MODULATES ACETYLCHOLINE RELEASE IN PREFRONTAL CORTEX: IMPLICATIONS FOR SCHIZOPHRENIA. Bruno [1], J.P.; Zmarowski [1], A.; Pellicciari [2], R.; Schwarcz [3], R. [1]Depts. of Psychology and Neuroscience, The Ohio State University, Columbus, OH; [2]Chimica e Technologia del Farmaco, University of Perugia, Perugia, Italy; [3]Maryland Psychiatric Research Center, Maryland School of Medicine, Baltimore, MD. Kynurenic acid (KYNA) is an astrocyte-derived metabolite of the kynurenine pathway of tryptophan degradation. KYNA levels are elevated in the frontal cortex of individuals with schizophrenia (SZ). Endogenous KYNA functions as a neuroinhibitory gliotransmitter due to its ability to potently antagonize the alpha7 nicotinic acetylcholine (ACh) receptor in rodents. KYNA levels modulate extracellular levels of dopamine and glutamate in several brain regions, including prefrontal cortex (PFC), and this may contribute to dopaminergic and glutamatergic dysfunction in SZ. There is also considerable evidence for abnormal cortical cholinergic transmission in SZ, which is likely to play a role in the cognitive deficits accompanying the disease. Thus, we determined if KYNA modulates extracellular levels of cortical ACh and affects cognitive behavior. KYNA levels were elevated via local perfusion of KYNA (100 nM) or following systemic administration of its precursor kynurenine (50 mg/kg, ip). KYNA levels were reduced using local perfusion of UPF 874 (5 mM), a specific inhibitor of KYNA's major biosynthetic enzyme, kynurenine aminotransferase II. The KYNA-based modulation of basal and stimulated (following systemic amphetamine, 0.2 mg/kg, ip) ACh levels in PFC were measured using in vivo microdialysis in freely-moving rats. We also determined the effects of systemic kynurenine on performance in a set-shifting task that depends upon intact frontal cortical function. Results show that KYNA levels bi-directionally modulated cholinergic transmission in PFC, with increases and decreases in cortical KYNA leading to reductions and elevations in basal ACh levels, respectively. The elevation in cortical ACh seen following local UPF 874 application was completely blocked by co-perfusion with 100 nM KYNA. Systemic administration of kynurenine also reduced basal levels of cortical ACh, as well as completely blocked stimulated ACh release seen following amphetamine. Finally, systemic kynurenine markedly impaired the ability of rats to perform an extra-dimensional shift in the set-shifting task. These findings extend the emerging role of glia-neuron interactions in normal brain function and disease. The data are specifically relevant to the neurochemical abnormalities in SZ and suggest a potent, novel therapeutic strategy for treating the accompanying cognitive deficits.

UNUSUAL BACKGROUND GENES IN THE BTBR T+tf/J MOUSE MODEL OF AUTISM INCLUDE A KYNURENIC ACID METABOLIC ENZYME Crawley, J.N.; Laboratory of Behavioral Neuroscience, National Institute of Mental Health, Bethesda, MD 20892-3730 USA The BTBR T+tf/J (BTBR) inbred strain of mice incorporates behavioral traits relevant to the three diagnostic symptoms of autism. BTBR displays low reciprocal social interaction as juveniles and adults, lack of sociability in our automated three-chambered social approach task, reduced social transmission of food preference, unusual pup separation vocalizations, resistance to change in a spatial habit on the Morris water maze, unusual exploration in a hole board task, and repetitive self-grooming, as compared to the commonly used inbred strain C57BL/6J (B6) (McFarlane et al., 2007; Yang et al., 2007; Moy et al., 2008; Scattoni et al., 2008). General health, motor functions, sensory abilities, and scores on anxiety-related tests were within the normal range in BTBR, ruling out the likelihood that physical or procedural artifacts could explain the autism-like phenotypes. Search of available genetic databases for single nucleotide polymorphisms (SNP) in BTBR versus B6 revealed a nonsynonymous coding region SNP in BTBR in the gene for Kmo, the gene encoding kynurenine 3-hydroxylase. This enzyme regulates the metabolism of kynurenic acid, a neurochemical that is synthesized in glia. Kynurenic acid acts as an antagonist at glutamate and nicotinic receptors, and has been implicated in schizophrenia and Huntington's disease (Schwarcz and Pellicciari, 2002). Kynurenic acid appears to modulate neuroprotection, dopamine release, and the formation of dendritic spines. Ongoing studies are investigating the biological importance of the Kmo mutation in the BTBR mouse brain and in autism.

OLIGODENDROGLIAL AND MYELIN DEFICITS IN SCHIZOPHRENIA: IMPLICATIONS FOR SALTATORY SIGNAL CONDUCTION AND THE DISCONNECTIVITY SYNDROME. Haroutunian, V.; Dracheva, S.; Katsel, P. and Davis, K.L. Department of Psychiatry, The Mount Sinai School of Medicine, New York, NY 10029. The disconnectivity syndrome hypothesis of schizophrenia suggests that communication between multiple brain circuits and regions may be disrupted. Microarray studies of postmortem brain analyzed gene expression in 15 different brain regions derived from antemortem assessed and diagnosed persons with schizophrenia and controls. The superior temporal gyrus, cingulate gyrus and hippocampus evidence the greatest numbers of abnormally expressed genes and have been classified as brain regions of transcriptional vulnerability in schizophrenia. Gene ontology categorization and biological pathway analyses have suggested that gene classes associated with oligodendrocytes and myelin function were among the most profoundly affected in schizophrenia. Quantitative PCR, Western blot and additional microarray studies have validated these oligodendrocyte and myelin associated findings in independent cohorts. At least some of the affected genes are associated with the regulation of axoglial contacts, axon caliber and the integrity of functional elements involved in signal propagation, intermodal length and the distribution of Na and K channels at the nodes of Ranvier. Recent studies derived from these analyses have also suggested alterations in cell cycle associated genes and proteins in schizophrenia. Experiments in transgenic animal model systems have linked these cell cycle gene and protein abnormalities to oligodendroglial compartments and have suggested the ectopic cell cycle reentry of postmitotic glia. The confluence of emerging evidence from genetic, neuroimaging, postmortem and animal model studies shows that myelination and oligodendroglial abnormalities are major components of the neurobiology of schizophrenia and suggest that re-evaluation of some long-held hypotheses and beliefs regarding the biological substrates of schizophrenia may be warranted.

NEURON-GLIA INTERCOMMUNICATION DURING NEUROINFLAMMATION ASSOCIATED WITH ALZHEIMER'S DISEASE AND OTHER NEURODEGENERATIVE DISORDERS. Wenk, G.L.; Brothers, H.M.; Cerbai, F.; Marchalant, Y. Dept Psychology, The Ohio State Univ., Columbus, OH, 43210 A major problem in the development of age-associated neurodegenerative disorders may be a failure of the glia to convert spontaneously from the pro-inflammatory activation state to an anti-inflammatory activation state, leading to excessive neuronal injury and cell loss. Neurons may maintain glia in a quiescent state in the young, uninjured brain. A failure in this intercommunication may result in the inappropriate activation of microglia and increased levels of cytokines and free radicals. With aging, the control of this intercommunication is crucial because inflammatory changes are closely related to the clinical manifestations of many age-related diseases. In the current study, young male rats were chronically infused with LPS into the fourth ventricle for 1, 4 or 8 weeks. We examined for changes in a negative regulator of microglia activation, CD200. Microglia activation correlated with poor performance in the Morris Water Maze task and loss of tyrosine hydroxylase immunoreactive cells in the substantia nigra. Memantine treatment restored the balance of these factors in LPS-infused rats and restored the number of dopamine neurons in the nigra. NMDA receptors are not located on microglia, indicating that memantine's actions are indirect through its effect upon neurons. A better understanding of the role of the NMDA receptor and the biomolecules that control the activation states of microglia may lead to an effective approach for regulating chronic inflammatory diseases in humans. Support: NIH AG10546, Merz Pharmaceuticals

11:00-12:15 Oral Session 2: Learning, Memory and Motor Systems. Chairs: Stefan Brudzynski and Evelyn Field

NSAID TREATMENT CAN REVERSE INFLAMMATION-INDUCED DEFICITS IN ADULT NEUROGENESIS AND MEMORY Brandi K. Ormerod1 ; Star W. Lee2; Theo D. Palmer2 1Biomedical Engineering Dept at the University of Florida and 2Neurosurgery Dept and Neuroscience Program at Stanford University Human and animal cognition suffers after the acute symptoms of transient illness resolve, but few insights or even studies regarding the mechanisms mediating this symptom exist. Spatial information is managed by the hippocampal formation, which (along with the olfactory bulbs) exhibits the rare ability to add new neurons throughout life. The degree of neuron addition has been positively correlated with hippocampal integrity, often measured by Morris water maze performance, in adult rodents. The present study shows that a 72-hr mild 'flu-like' illness immediately reduces hippocampal neurogenesis in adult mice. This immediate reduction in new neurons translates into a depletion of maturing new neurons that should be integrating into the circuitry, weeks later. This long term deficit also coincides with a time that mice exhibit memory problems in the Morris water maze. Nonsteroidal anti-inflammatory drug (NSAID) treatment for two weeks during and immediately after illness protects neurogenesis and memory, indicating that the innate proinflammatory response is responsible for these deficits. Our investigation of the NSAID mechanism of action demonstrated that selective Cox-2 inhibition unexpectedly aggravated the memory deficits and caused impairments even in the absence of illness while selective PPARγ activation protected neurogenesis and memory from neuroinflammation. These data indicate that alterations in neurogenesis contribute to illness-induced memory impairment, which can be aggravated or alleviated depending upon the NSAID therapy used.

MAGNETIC RESONANCE IMAGING (MRI) OF THE DEVELOPING HUMAN BRAIN: HAND USE AND SEXUAL DIMORPHISMS. Almli, C.R., Developmental Neuropsychobiology Laboratory, Depts. of Neurology, Psychology, Programs in Occupational Therapy, Neuroscience, Washington University Medical School, St. Louis, MO 63108 USA. Magnetic Resonance Imaging (MRI) is becoming a powerful tool for studying anatomical (aMRI) and functional (fMRI) development of the human brain in health and in disease. This presentation reports on an aMRI study of sexual dimorphisms during development, and on an fMRI study of fine motor control. First, a multi-center project (The NIH MRI Study of Normal Brain Development) as been mapping aMRI of the developing brain of normal, healthy human infants, children and adolescents from birth through 18-plus years of age (i.e., 500 children with 1,000 non-sedated aMRI brain scans). Subjects also received comprehensive neurobehavioral testing and growth assessments, and brain scan analyses were controlled for demographic variables (e.g., IQ, family income). Second, newer studies in my laboratory are focusing on task-related, functional neuroimaging (i.e., fMRI during finger tapping tasks) to study hand use of children from 4 to 7 years of age. Developmental results of these two studies include growth curves for cortical lobes and other regional volumes (e.g., thalamus, caudate and putamen, brainstem and cerebellum, gray and white matter), sexual dimorphisms in subcortical and cortical brain development, and, fMRI comparisons of BOLD activations of early school-age children versus young adults performing a fine motor control task.

ELECTRICAL STIMULATION OF THE POSTERIOR HYPOTHALAMIC NUCLEUS AMELIORATES 6-OHDA INDUCED AKINESIA. [1]Young, C.K.; [1]Koke, S.J.; [2]Kiss, Z.H.; [1]Bland B.H. [1]Dept. of Psychology, [2]Dept. of Clinical Neurosciences, University of Calgary, Canada. The use of deep brain stimulation (DBS) in the context of Parkinson's disease (PD) treatment has been extremely efficacious. However, the clinical benefits of DBS are mainly seen in the amelioration of tremors and rigidity whereas bradykinesia and akinesia remain mostly resistant to traditional DBS protocols. Recently, we have shown that DBS of the posterior hypothalamic nucleus (PH) in rats can reverse haloperidol induced akinesia and restore avoidance behaviour in an active avoidance paradigm. In this study, we tested the potential therapeutic effects of PH DBS in the 6-hydroxydopamine (6-OHDA) model of PD. Bilateral cannulae were implanted to target the medial forebrain bundle (mfb) prior to active avoidance training. After the animals had reached criterion (8/10 consecutive avoidances under 10s), 10 trials with PH stimulation and 10 trials without PH stimulation were taken as pre-lesion data immediately prior to 6-OHDA injections into the mfb. The animals demonstrated a 100% success rate and a <3s avoidance latency. Three days after the 6-OHDA lesion, animals were tested again (10/10, PH stimulation/no PH stimulation trials). The results revealed an almost total elimination (i.e. latency >10s and success rate <10%) of avoidance behaviour after 6-OHDA treatment, which was subsequently ameliorated by electrically stimulating the PH (latency <6s and success rate >80%). This study provides further support for the clinical usage of PH DBS as an efficacious treatment of PD and potentially other movement disorder –related akinesia.

MOTOR-SKILL LEARNING IN A NOVEL RUNNING-WHEEL TASK: CRITICAL ROLE FOR D1 DOPAMINE RECEPTORS IN THE STRIATUM. Steiner, H.; Willuhn, I. Dept. of Cell. and Mol. Pharmacology, RFUMS/Chicago Medical School, North Chicago, IL 60064, USA. Dopamine receptors regulate processes of procedural learning mediated by the sensorimotor striatum. Our previous studies showed that the indirect dopamine receptor agonist cocaine alters gene regulation in the striatum associated with motor-skill learning in a novel running-wheel paradigm. We investigated the effects of cocaine and the D1 receptor antagonist SCH-23390 on wheel-skill learning. During training rats learn to control/balance the wheel in order to run at the bottom of the wheel (wheel skill). This skill memory lasts for several months even after limited training (1-2 sessions). Cocaine (25 mg/kg) given before the training session tended to attenuate this skill learning despite increasing the amount of running (practicing). Similarly, systemic administration of SCH-23390 (3-10 ∝g/kg) before the training attenuated such skill-learning (without affecting the amount of running). However, when combined, cocaine completely reversed the inhibition of wheel-skill learning produced by the lower dose of SCH-23390 (3 ∝g/kg). In contrast, cocaine plus the higher dose of SCH-23390 (10 ∝g/kg) normalized skill performance 1-6 days after the training, but these rats lost their improved wheel skill by day 18 after the training. Similar effects were produced by SCH-23390 (0.3-1 ∝g) infused into the striatum. Our findings indicate that cocaine interferes with normal motor-skill learning and that such skill learning is dependent on optimal D1 receptor signaling. Moreover, D1 receptors in the striatum appear to be critical for consolidation of long-term skill memory. Supported by USPHS grant DA011261.

4:00-6:00 Symposium 4: Animal modeling of cognition: Relevance to schizophrenia. Chair: Jared W. Young.

FINDING AND DEVELOPING COGNITION ENHANCERS FOR SCHIZOPHRENIA: IS THERE A NEEDLE IN THE HAYSTACK? Sarter, M., Department of Psychology, University of Michigan, Ann Arbor, MI 48109 USA. The development and validation of animal models of the cognitive impairments of schizophrenia has remained a challenging yet pressing subject. I will review evidence from a series of experiments concerning an animal model that dissociates between the disruption of attentional capacities during acute illness periods and the cognitive load-dependent impairments that characterize periods of remission. The model focuses on the long-term attentional consequences of an escalating dosing pretreatment regimen with amphetamine (AMPH). Acute illness periods are modeled by the administration of AMPH doses that do not affect the attentional performance of control animals and are characterized by loss of cognitive task control and the "freezing" of performance-associated cortical acetylcholine (ACh) release at pre-task levels. During periods of remission, in the absence of AMPH-challenges, performance is mediated via abnormally high levels of cortical ACh release, indicative of the elevated attentional effort on the basis of which performance is maintained. Furthermore, and corresponding with clinical evidence, attentional performance during remission periods is exquisitely vulnerable to distractors, reflecting the limited capacity for coping with additional demands for top-down control and the underlying abnormalities in fronto-mesolimbic-basal forebrain circuitry. Contrary to the widespread view that there are no cognition enhancers that could be used to test the predictive validity of animal models of the cognitive symptoms of schizophrenia, there is robust evidence that administration of low doses of haloperidol and clozapine, defined on the basis of <50% dopamine D2 receptor occupation, produce moderately beneficial cognitive effects in schizophrenic patients (so there are the needles in the haystack). This animal model detects these beneficial cognitive effects of such treatments. The usefulness and limitations of this model for research on the neuronal basis of the cognitive impairments in schizophrenia and for drug finding efforts are discussed. Supported by PHS Grants MH080426, MH080332 and KO2MH01072.

CORTICO-THALAMIC-STRIATAL CIRCUITS UNDERLYING BEHAVIORAL FLEXIBILITY. Floresco, S.B. The ability to use information flexibly and execute appropriate adaptive behaviors in response to changes in one's environment is an executive function mediated in part by the prefrontal cortex (PFC). Impairments in different forms of behavioral flexibility are associated with a number of psychiatric disorders, including schizophrenia. Recent work from our laboratory has elucidated some of the specific contributions that different cortical-subcortical circuits make to dissociable components of set-shifting, when an organism must cease attending to previously relevant stimuli and use a novel strategy to obtain a goal. One circuit that includes the PFC and the mediodorsal thalamus plays a selective role in suppressing the use of previously relevant strategies. Another pathway linking the thalamus to the nucleus accumbens (NAc) facilitates the acquisition of a novel strategy, whereas separate cortico-striatal circuits mediate the maintenance of a novel strategy. Mesocorticolimbic dopamine also makes an essential contribution to this form of behavioral flexibility, although the receptor mechanisms through which dopamine exerts its effects differs between brain regions. Blockade of D1 or D2 receptors in the PFC induces perseverations, whereas only D1 receptor activity in the NAc appears to be required for the maintenance of novel strategies. Moreover, excessive stimulation of dopamine receptors in the NAc, but not the PFC also impedes set-shifting. These data indicate that set-shifting is mediated by a distributed neural circuit, with separate neural pathways contributing dissociable components to this type of behavioral flexibility. In so doing, they provide important insight into the neural pathology that underlies executive dysfunction in psychiatric disorders where impairment in behavioral flexibility is a prominent symptom.

COGNITIVE CORRELATES TO PREPULSE INHIBITION IN MAN: APPLICABLE FOR RESEARCH IN RODENTS? Risbrough, V.B., Dept. of Psychiatry, University of California, San Diego, CA, 92093-0804 USA. Across species, presentation of a non-startling acoustic "prepulse" 30-300 ms before a startling stimulus reduces the magnitude of the startle reflex. This phenomenon is termed "Prepulse Inhibition" (PPI) of startle, and is used to measure sensorimotor gating. PPI is reduced in a number of neuropsychiatric disorders, many of which are characterized by pathology in the cortical-striatal loop, including schizophrenia, Huntington's disease, and obsessive compulsive disorder. Graham (1975) suggested that PPI can measure information processing, a construct of "automatic" attention in which an organism filters out extraneous stimuli during active stimulus processing. There is some evidence that PPI reflects automatic or "pre-attentional" mechanisms which may be orthogonal to controlled attentional systems. There are conflicting reports however, that PPI and other measures of sensorimotor or sensory gating are required for or linked to specific cognitive domains. In humans, deficits in PPI do not appear to be linked to cognitive deficits as assessed by paper-pencil scales, however there may be a link between PPI and speed of processing or response time, as well as measures of global functioning. In animals PPI appears to be orthogonal to other pre-attentional and some cognitive tasks. This presentation will discuss the following questions: (1) what cognitive domains are associated with PPI performance in animals and humans, (2) is PPI predictive of known cognitive disrupters and enhancers, (3) can it probe the integrity of neural systems required for cognitive tasks in rodents and humans? Supported by CESAMH, NARSAD, MH074697

THE RODENT CONTINUOUS PERFORMANCE TEST: IMPACT FOR TRANSLATIONAL DRUG DISCOVERY. Young, JW.; Geyer, MA. Dept. of Psychiatry. University of California, San Diego, CA, 92103, USA. Attentional dysfunction is apparent in various neuropsychiatric disorders including schizophrenia and Alzheimer fs disease. Indeed, attention/vigilance to closely related to functional disability in these patients and is among the leading targets for developing pro-cognitive medications. Attention in humans is frequently assessed using the continuous performance test (CPT), yet there are no directly analogous paradigms for assessing genetic and pharmacological influences on rodent attention. We describe a rodent (*r*)CPT that models the human (*h*)CPT, providing a measure of vigilance commonly reported in human studies, A Œ. C57BL/6J and DBA/2J mice were trained in the *r*CPT and the 5-Choice Serial Reaction-Time Task (5CSRTT), with C57BL/6J mice also trained in a simple reaction-time (RT) task involving 1-choice (1CSRTT). DBA/2J mice exhibited inferior accuracy compared to C57BL/6J mice in the 5CSRTT ($p<0.05$) but not the *r*CPT ($p>0.05$), suggesting greater stimulus control when required to attend to both relevant and irrelevant stimuli in the *r*CPT. Significant A prime differences in the *r*CPT ($p<0.05$) however, provide direct evidence of inferior vigilance in DBA/2J. DBA/2J mice also exhibited a greater vigilance decrement across trial number compared to C57BL/6J mice. Increased RTs with increased attentional load (1CSRTT<5CSRTT<*r*CPT; $p<0.05$) was also observed. In conclusion, DBA/2J mice exhibited significantly inferior performance compared to C57BL/6J mice in a sustained attention vigilance measure reported in human studies. Both RT differences and vigilance decrements provide validity for the *r*CPT as a test of sustained attention analogous to the *h*CPT.

6:00-8:30 Poster Session 2

Learning and Memory

54. EXPLICIT DISASSOCIATION OF A CONDITIONED STIMULUS (CS) AND UNCONDITIONED STIMULUS (US) DURING EXTINCTION TRAINING REDUCES BOTH TIME TO ASYMPTOTIC EXTINCTION AND SPONTANEOUS RECOVERY OF A CONDITIONED TASTE AVERSION (CTA). Mickley, G. A.; DiSorbo, A.; Wilson, G.N.; Huffman, J., Bacik, S.; Hoxha, Z.; Biada, J.M.; Kim, Y.-H. The Neuroscience Program and The Department of Psychology, Baldwin-Wallace College, Berea, OH 44017 USA. CTAs may be acquired when an animal consumes a novel taste (CS) and then experiences the symptoms of poisoning (US). When later given a choice between the poisoned taste and water, the animal will avoid the taste previously associated with malaise. This aversion may be extinguished by repeated exposure to the CS alone. However, following a latency period in which the CS is not presented, the CTA will spontaneously recover (SR). Thomas et al. (2005) have used an explicitly unpaired (EU) procedure to thwart renewal of a conditioned emotional response (CER) following extinction. We applied similar procedures to the CTA paradigm. Sprague-Dawley rats acquired a CTA [3 pairings of oral saccharin (SAC) and i.p. lithium chloride (LiCl)] followed by extinction training (EXT) consisting of either (a) CS-only exposure or, (b) exposure to SAC and LiCl on alternate days (i.e., explicitly unpaired: EU). Both extinction procedures resulted in 90%+ reacceptance of SAC although the EU-EXT procedure significantly decreased the time necessary for rats to reach this criterion (compared to CS-only controls). Rats were subsequently tested for SR of the CTA upon re-exposure to SAC following a 30-day latency period of water drinking. Rats that underwent the CS-only extinction procedure exhibited a significant suppression of SAC drinking during the SR test (as compared to their SAC drinking at the end of extinction). However, animals in the EU extinction group did not show such suppression in drinking compared to CS-only controls. These data suggest that the EU-EXT procedure may be useful in reducing both time to EXT and the spontaneous recovery of fears. The findings are clinically relevant as we seek the development of treatments for deficits in fear extinction (e.g., PTSD, phobias). Supported by NIMH grant: 2-R15-MH063720-03.

55. MUSCARINIC BLOCKADE IN THE ENTORHINAL CORTEX PREVENTS ACQUISITION OF INATTENTION TO IRRELEVANT STIMULI: RELEVANCE TO SCHIZOPHRENIA. Barak, S.; Weiner, I. Dept. of Psychology, Tel Aviv University, Israel. Latent inhibition (LI) is a cross-species phenomenon manifested as a poorer conditioning of a stimulus seen when the stage of conditioning is preceded by a stage of repeated nonreinforced pre-exposure to that stimulus, and is considered to index the ability to ignore, or to in-attend to, irrelevant stimuli. Several studies have indicated that the entorhinal cortex (EC) plays a critical role in LI. EC lesion or temporal inactivation during the pre-exposure stage disrupts LI, suggesting that the EC subserves the acquisition of inattention to the pre-exposed stimulus. Our recent finding that systemic administration of the muscarinic antagonist scopolamine also disrupted LI when injected in the pre-exposure but not in the conditioning stage, has led us to test the hypothesis that cholinergic transmission in the EC is responsible for the effects of EC manipulations on LI. Scopolamine (1 or 10 µg per hemisphere) was infused into the EC in the pre-exposure stage, the conditioning stage or in both stages. We found that muscarinic blockade in the EC disrupted LI when introduced in pre-exposure or in both pre-exposure and conditioning, but not if confined to conditioning. While cholinergic innervation of the EC has long been postulated to be involved in the attention to, and encoding of, novel stimuli, our results provide first evidence that it also plays a crucial role in the development of inattention to stimuli. Moreover, our results suggest that muscarinic receptors in the EC mediate acquisition of inattention. Thus, muscarinic dysfunction in the EC may underlie not only working memory deficits and impaired ability to maintain attention to significant stimuli, but also distractibility caused by impaired ability to in-attend irrelevant stimuli, seen in disorders such as schizophrenia.

56. INTRANASALLY ADMINISTERED VCP IMPROVES PAIRED-ASSOCIATION LEARNING IN MO/HU APPSWE PS1δE9 MICE IN A NOVEL CHEESE-BOARD MAZE TASK. Kulkarni, A.1, 2; Kellaway, L.2; Govender, D3; Kotwal, G.4 1Division of Medical Virology, 2Division of Neuroscience, and 3Division of Anatomical Pathology, IIDMM, FHS, University of Cape Town, South Africa. 4Kotwal Bioconsulting, LLC, Inflamed Inc., Louisville, KY, 40241, USA. The complement system is at the core of the pathophysiology of Alzheimer's disease (AD), the most prevalent brain disorder. However, currently there is no therapeutic agent targeting the complement components available on the market. To develop complement based CNS therapeutics, vaccinia virus complement control protein (VCP), a complement regulatory protein of viral origin and curcumin, an anti-inflammatory ingredient of turmeric, were administered intranasally in Mo/Hu APPswePS1δE9 mice (11-14 months; Jackson laboratories). A novel cheese-board maze model based on odour and object discrimination was developed to compare the paired-association learning abilities of the above groups to that of saline treated transgenic and non-transgenic control groups. The maze tasks involve the mouse having to discriminate between the reward and non-reward flags by associating the odour of the flag (using either cinnamon or cumin) and extra-maze spatial cues to get to the reward (sugar pellets) located at the reward flag. At the end of the training session, probe trials were conducted with and without flags and/or hiding the extra-maze cues. The data was digitally recorded and analysed for various behavioural parameters (e.g. time to visit the reward flag, time spent near flags, etc.) by using EthoVision and STATISTICA software. The results suggested that VCP shows a better paired-association learning ability in APPswe transgenic mice, compared to curcumin. Brain and CSF samples also collected from these mice are being used to study the distribution of intranasally delivered agents and/or the amyloid staining pattern in the respective treatment groups.

57. CRANIAL IRRADIATION IMPAIRS NEUROGENESIS AND COGNITION DISTINCTIVELY IN JUVENILE AND ADULT MICE. Lee, S.W.; Palmer, T.D. Dept of Neurosurgery. Stanford University, Stanford, CA 94305 USA. Brain tumors are treated with surgery, chemotherapy, and cranial irradiation. While cranial irradiation is necessary for effective tumor ablation, it is also associated with persistent cognitive deficits that gradually worsen with time. These deficits are most dramatic in children and one of the early and prominent signs is difficulty with learning and memory tasks that are largely mediated by the hippocampus. The hippocampus is a late-developing area where neural stem and progenitor cell-mediated neurogenesis continue to play a significant role in postnatal neural development. Neural progenitor cells in the hippocampus also provide homeostatic and cell replacement functions in the adult and it has been proposed that radio-ablation of stem cell activity may contribute to deficits in learning and memory. In mouse models of cranial irradiation there is a permanent reduction in progenitor cell activity and neurogenesis in the hippocampus following irradiation. Here, we have investigated the impact of cranial irradiation on neurogenesis and cognition in juvenile and adult mice. By examining performance in spatial reference memory, delayed matching-to-place in the water maze, and context fear conditioning and have found that a distinct subset of learning and memory functions are uniquely associated with the partial ablation of hippocampal neurogenesis following cranial irradiation.

58. FUNCTION OF THE CHOLINERGIC AND BETA-ADRENERGIC SYSTEMS DURING ACQUISITION, CONSOLIDATION AND RETRIEVAL OF LONG TERM MEMORY OF ODOURS WITH DIFFERENT EMOTIONAL CONTENT. Miranda, M.I.; García, D.; Ortiz-Godina, F. Instituto de Neurobiología, Universidad Nacional Autónoma de México, Campus Juriquilla, Qro. México. The cholinergic system has an important role in regulating memory formation for different novel stimuli by interactions with other neurotransmitter systems. Also, acetylcholine and norepinephrine have been implicated during different kinds of social recognition that involves olfactory memory formation. For example, blockade of muscarinic and beta-adrenergic receptors has been shown to impair short term olfactory memory during social recognition as well for non relevant odour memory. However, previous studies have not explicitly compared the role of cholinergic and adrenergic modulation in long term memory for social or relevant odour versus incidental odour stimuli. In this work, we studied the function of muscarinic and beta-adrenergic receptors during acquisition and/or consolidation of a novel odour and during the retrieval of a familiar odour. The effect of systemic injections, of scopolamine and propranolol before and after presentation of odour estrus, urine odour or mint odour, were evaluated by a long term odour habituation task. The results demonstrated that scopolamine injections disrupted the memory consolidation for novel odours but not their acquisition, despite their emotional content. However, propranolol injections did not have any effect during acquisition or consolidation but significantly disrupted the retrieval for long term memory of both odour stimuli. These results confirm that muscarinic receptors are required during novel odour recognition and indicate that cholinergic activity is necessary during olfactory consolidation memory. Furthermore, the beta-adrenergic system could play an important role in familiar recognition odours regardless of the emotional content of the odour stimuli. Support contributed by: PAPIIT IN201308, CONACyT C54524, 46161M, 46754Q. Thanks to Mireya Romero, Juan Pablo McGregor, Raúl Paredes, Shaun Harris.

59. SEX STEROID HORMONE ESTROGEN AND WORKING MEMORY FOR EMOTIONAL FACIAL EXPRESSIONS. Gasbarri, A.*1; Pompili, A1; d'Onofrio, A1; Cifariello, A1; Falconieri,D.1; Tavares, M.C.2 ; Tomaz, C.2 . Dept. Biomed Sci & Technol,Univ. L'Aquila, Italy1. Dept. Physiol. Sci, Lab. Neurosci. & Behav, Univ. Brasília, Brazil 2. The sex steroid hormone estrogen affects the nervous system in many ways that extends beyond its role in the control of the reproductive function and recent studies evidenced important issues regarding the hormonal influence on cognitive functions, such as learning and memory. Taking into account that women's performance in memory tasks can fluctuate according to the hormonal levels across the menstrual cycle, the performance in a Delayed Matching-to-Sample (DMTS) working memory task for emotional facial expressions was evaluated in young women, in the different phases of the menstrual cycle,. Our findings suggest that high levels of estradiol in the follicular phase could have a negative effect on DMTS with emotional stimuli. Moreover, compared to the menstrual phase, in the follicular phase the percent of errors was significantly higher for sadness and disgust facial expressions. The evaluation of the times of answer for each emotional facial expression showed a statistical difference between follicular and luteal phases, relatively to sadness. Moreover, high levels of estradiol in the follicular phase can impair the performance of working memory for selective facial expressions suggesting that, during the menstrual phases at high conception risk, women give less importance to emotional expressions with irrelevant reproductive significance, such as sadness and disgust. Our data show that fluctuations of ovarian hormones across the menstrual cycle influence several behaviors and could help in individuating therapies for the treatment of disturbances linked to menstrual cycle phases and menopause in women.

60. 5-HT7 ANTAGONIST SB-269970 AND ITS ROLE IN THE MODULATION OF WORKING AND REFERENCE MEMORY IN RATS. Gasbarri, A.*1; Cifariello, A.1; Pompili, A.1, Arnone, B1 ; Meneses, A.2. Dept. Biomed Sci & Technol,Univ. L'Aquila, Italy1, Depto. de Farmacobiología, CINVESTAV, Mexico It has been established that serotonergic pathways project to cerebral areas involved in learning and memory and that serotonin (5-HT) receptor agonists and antagonists modify these processes. Indeed, most of the 5-HT receptors characterized so far, i.e., 5-HT1 through 5-HT7, show a regional distribution in brain areas involved in learning and memory, such as hippocampal formation (HF), amygdala and cortex. Although 5-HT7 receptor biological functions are still to be clarified, it was recently suggested that it may play a role in the control of learning and memory processes. The aim of our study was to assess the role of 5-HT7 receptors antagonist SB-269970 on working and reference memory in a radial arm maze task, utilizing a two-phase procedure, comprising an acquisition and test phase, conducted to evaluate working and reference memory, respectively. Our results showed that 5-HT7 receptors antagonist SB-269970 improved memory, decreasing the number of errors in test phase and, thus, affecting reference memory, while no effects were observed in working memory. These results could be explained taking into consideration the specific localization of 5-HT7 receptors in the CNS. In fact, high concentrations of 5-HT7 receptors were found in the HF, which exerts an important role on reference memory, while relatively low concentrations were present in the prefrontal cortex, involved in working memory. Thus, 5-HT7 receptor blockade had procognitive effect, when the learning task implicated a high degree of difficulty. This conclusion has a major implication in the context that 5-HT receptors play an important role under amnesia states or when the learning is complex.

61. EMOTIONAL FACIAL EXPRESSIONS IN CAPUCHIN MONKEY (CEBUS APELLA). Tavares, M.C.1; d'Onofrio, A2; Marchetti A2; Abreu C.T.1; Gasbarri, A.2; Tomaz, C.1. Dept. Physiol. Sci, Lab. Neurosci. & Behav, Univ. Brasília, Brazil1.Dept. Biomed Sci & Technol, Univ. L'Aquila, Italy2. Non-human primates represent relevant models for the study of emotional face processing, because they share several cognitive and physiological characteristics with humans. Many studies have been focused on Capuchin monkeys (Cebus apella), since they exhibit a rich repertoire of facial expressions and body postures, and can readily solve the working memory (WM) tasks, such as the delayed non-matching to sample (DNMTS) task. In this study we developed a pool of 384 pictures of capuchin monkey (Cebus apella) faces, classified according to the emotional valence (positive/ pleasant, negative/unpleasant and neutral/indifferent), to examine if WM can benefit from the emotional content of visual stimuli in a DNMTS task. Seven adult capuchin monkeys were tested with a computer system and touch screen. Geometric figures (control) and co-specific faces pictures were used as stimuli. The subjects obtained a similar performance to positive, negative and neutral pictures. However, the monkeys performed above the upper confidence limits around chance to all kinds of stimulus, showing that they are able to learn the tests using emotional faces. Furthermore, the capuchin monkeys had much better performance when using geometric figures, compared with the co-specific pictures. This preliminary study yielded findings that are of relevance for a better understanding of the influences of emotional expressiveness on memory, and indicate the possible usefulness of applying the paradigm utilized in this study to investigate emotional working memory in non-human primates.

62. HIPPOCAMPAL NR2B-CONTAINING NMDA RECEPTORS ARE ESSENTIAL FOR SPATIAL MEMORY ENCODING Brigman, J.L.; Delpire, E.; Holmes, A. Laboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, Rockville, MD; Dept. of Anesthesiology and Molecular Physiology & Biophysics, Vanderbilt Univ. Medical Center, Nashville, TN Activation at the N-methyl-D-aspartate receptor (NMDAR) initiates a cascade of molecular events that underlie synaptic plasticity and subserve learning and memory. NMDAR are heteromers composed of a NR1 subunit and one or more NR2 (NR2A-NR2D) subunits. NR2A and NR2B subunits are both highly expressed in hippocampus, but contribute distinct physiological and molecular properties to NMDAR. A major unresolved issue is the relative contribution of NR2A and NR2B to hippocampal-mediated forms of learning and memory. We assessed mice in which NR2B was excised (post-development) in the pyramidal cell layer of the dorsal hippocampus, via a αCaMKII-driven Cre/LoxP system. Previous studies have shown that intra-hippocampal administration of subunit-non-selective NMDAR antagonists impairs spatial learning in the Morris water maze test, but not on other learning tasks such as Pavlovian fear conditioning. We found that hippocampal-NR2B knockout (KO) mice were markedly impaired on a version of the Morris water maze that requires the formation of a spatial map of distal cues surrounding the maze. By contrast, KO mice were no different from wild-type (WT) controls on a non-spatial, hippocampal-independent version in which the escape platform is visibly-cued. Pavlovian fear conditioning was also normal in KO mice. These data demonstrate a selective deficit in the encoding of spatial memories in mice lacking NR2B subunit in dorsal hippocampus and provide the clearest evidence to-date that NR2B-containing NMDAR are necessary for memory formation. This finding has implications for elucidating the pathophysiology and treatment of cognitive impairment in neuropsychiatric disorders ranging from Alzheimer's disease to schizophrenia.

63. RAPID EFFECTS OF ESTROGEN RECEPTOR ALPHA AND BETA AGONISTS ON LEARNING AND MEMORY. Phan, A.[1,2]; Lancaster, K.E.[1]; MacLusky, N.J.[1]; Choleris, E.[2] [1]Dept. of Biomedical Sciences, [2]Dept. of Psychology. University of Guelph, Guelph, ON. N1G 2W1 Canada. Estrogens play a role in learning and memory, although results are inconsistent, with estrogens improving, impairing or having no effect on learning/memory. This may be the result of the activation of different estrogen receptors (ER), ERα and ERβ as well as membrane-associated ERs. Most research in the past has concentrated on the long term, genomic effects of estrogens (>24hrs). However, within the last decade, estrogens have been shown to have very rapid, short-term effects (<1-2hrs) on neuronal plasticity, including effects on neuronal morphology and electrophysiology. It is not known whether these rapid changes in neuronal plasticity have behavioral consequences. Therefore, we investigated the actions of an ERα agonist (PPT) and an ERβ agonist (DPN) on 3 estrogen-sensitive learning/memory paradigms. Two month old female, ovariectomized, CD1 mice were treated with PPT or DPN, then tested in social recognition (ability to recognize conspecific individuals), object recognition, or object placement paradigms. The paradigms were adjusted such that they were completed within 40min of the drug injections. PPT rapidly improved both social and object recognition compared to the vehicle control. DPN did not improve either type of recognition learning/memory and in fact seemed to impair social and/or object recognition. These data indicate that ERα and ERβ selective agonists may affect learning/memory, within minutes of the estrogen exposure. Supported by NSERC.

64. PERFORMANCE ON AN ATTENTIONAL SET-SHIFTING TEST INDUCES FOS EXPRESSION IN RAT PREFRONTAL CORTEX. Bondi, CO; Morilak, DA. Dept. Pharmacology. UTHSC, San Antonio, TX 78229 USA. Chronic stress is a risk factor for many psychopathological conditions, such as depression and anxiety disorders. Neuropsychological studies have shown prefrontal cortical cognitive dysfunction in patients with various neuropsychiatric disorders. The Wisconsin Card Sorting Test measures attentional deficits in such patients, whereas an attentional set shifting test (AST) tests these processes in rats in a series of discriminations for food reward, including stimulus reversals, and intra- and extradimensional (ED) set shifts. Lesions of mPFC impaired ED set-shifting, whereas OFC lesions impaired reversal learning. We found that elevating noradrenergic tone in rat mPFC enhances ED shifting, whereas chronic unpredictable stress (CUS) produces a deficit in ED shifting, prevented by concurrent NE reuptake blockade. Thus, to further investigate the specific anatomical substrates in rat PFC involved in manipulations that induce cognitive deficits or facilitation, we examined induction of Fos expression in PFC by performance on the AST. Rats were tested on the AST through either the second reversal or the ED stage, whereas home cage controls were given food reward and sacrificed with no testing. PFC sections (50∝m) of perfused brains underwent free-floating immunocytochemistry with a Fos antibody, visualized by a DAB reaction. Preliminary analyses indicate significant induction of Fos expression in PFC in animals performing on the ED set-shift relative to home cage controls. Ongoing studies investigate CUS-induced alterations of Fos expression in PFC during AST, as well as protective effects of concurrent NE reuptake blockade with the antidepressant drug, desipramine.

Reward and Addiction

65. ADOLESCENT SOCIAL DEFEAT ALTERS RESPONSES TO NOVELTY AND AMPHETAMINE IN ADULT RATS Burke, A.R.; Watt, M.J.; Renner, K.J.; Forster, G.L. Basic Biomed. Sci., Sanford School of Medicine, Univ. South Dakota, Vermillion SD USA. Adolescence is a period of essential fine tuning of mesocorticolimbic dopamine (DA) systems. Stress exposure during adolescence contributes to adult behavioral dysfunction, and is linked to adult psychiatric and addiction disorders. We have shown previously that rats experiencing adolescent social defeat exhibit altered anxiety behavior and reductions in medial prefrontal cortex (mPFC) DA levels as adults. Here we explored outcomes of adolescent social defeat on adult behavioral and neuroendocrine responses to amphetamine (Amp). Adolescent male rats (P38-43) were defeated for 5 days by an adult male, with controls placed in empty novel cages at matched times. As adults (P57-60), rats received an Amp injection (2.5 mg/kg, ip.) after a 30 min novel open field test, with behavior observed in the same context for 90 min thereafter. Previously defeated rats showed increased novel open field locomotion, suggesting adolescent defeat induces hyperlocomotion to novel contexts in adulthood. However, defeated rats exhibited reduced Amp-induced locomotion compared to controls. Plasma corticosterone (B) and monoaminergic responses to Amp were also examined. Following a second Amp injection 3 days later, defeated rats showed decreased B responses and did not exhibit the expected increase in mPFC DA, but showed greater DA responses in the nucleus accumbens core. Our results imply that defeat stress during adolescence alters behavioral and endocrine reactions to Amp in adulthood, which are paralleled by atypical DA responses in mesocorticolimbic systems implicated in addiction disorders. Support: NIH P20 RR15567 & NIDA RO1 DA019921.

66. EFFECT OF PERIADOLESCENT EXPOSURE TO NICOTINE ON ADULT RAT RESPONSE TO DIAZEPAM IN AN ELEVATED PLUS-MAZE. Anumudu, E.H.; Williams, H. L.; McMillen, B.A. Undergrad. Neurosci. Prog. and Dept. of Pharmacol. Toxicol., Brody School of Med. at East Carolina Univ., Greenville, NC 27834, USA. Research indicates an association between nicotine exposure during adolescence and increased responses to nicotine and other drugs of abuse in the adult. Adolescence represents a critical ontogenetic period during which nicotine exposure could alter adult responses to drugs of abuse. This experiment determined the effects of periadolescent exposure to nicotine in rats, on the adult response to another drug of abuse, diazepam. Rats were exposed to 0.4 mg/kg i.p. nicotine or vehicle daily from PD (postnatal day) 35-44 and additional rats from PD 60-69. At PD 80, after 1.0 mg/kg s.c. diazepam or vehicle 30 min pretreatment, all rats were observed for 5 min in an elevated plus-maze. This dose of diazepam is sub- or at threshold in this test. In the group treated at PD 35-44, there was a significant difference ($p < 0.05$) between the nicotine/diazepam rats and the other two groups of rats that were dosed with nicotine/vehicle or vehicle/vehicle (1.1 ±0.5 vs. 5.1 ±0.7 open arm entries and 10.5 ±6.6 vs. 53.9 ±13.5 sec in the openarm for veh/veh vs. nic/diaz treatments, respectively). However, statistical analyses of the data from the rat group that was exposed to nicotine at PD 60-69 revealed that between-group comparisons of the nicotine/diazepam, nicotine/vehicle and vehicle/vehicle sub-groups did not yield significant differences in their open arm activity. Thus, exposure to nicotine during the onset of adolescence affects the response of the young adult rat to a different drug of abuse in a non-reward based test. These data emphasize that the periadolescent period is a vulnerable developmental period.

67. INVOLVEMENT OF NUCLEUS ACCUMBENS DOPAMINE IN FAT OVEREATING IN RATS. Narikiyo, K.; Shiota, N.; Aou, S. Dept. of Brain Science and Engineering, Kyushu Institute of Technology, Kitakyushu, 808-0196 Japan. Limited access to highly palatable foods such as sugar or fat has been shown to induce overeating of them, which is similar to binge eating. Dopamine (DA) in the nucleus accumbens (NAc) is a possible target as underling mechanism of this eating behavior because it has similar characteristics to drug addiction. In this study, we investigated the relation of limited access induced fat intake enhancement and DA levels in rat NAc using microdialysis method. Male SD rats were used as subjects and a solid-type pure fat gshortening h was used as fat. To induce enhancement of fat intake, rats were allowed to access to fat 1h every 2nd day for 5 times. Regular chow and water were freely available all the time. By this schedule, rats showed gradual increases in fat intake and consumed approximately twice amount in 5th 1h fat access compared to 1st 1h. After this schedule, rats had implantation of guiding cannula aimed at NAc under anesthesia and had 1 day recovery period. On the DA measurement, rats had 20 min fat access to measure DA response to fat intake. We found that DA basal level was negatively correlated to increasing rate of fat intake (the 5th 1h fat intake / the 1st 1h fat intake) but not to the 1st or the 5th 1h fat intake itself. In addition, DA level to fat intake was increased in case of rats consumed smaller amount of fat but decreased in case of rats consumed larger fat, thus DA change negatively correlated to amount of fat intake. These indicate DA basal level and DA response to fat intake are involved in development and expression of fat overeating, respectively. These results might contribute to understanding of mechanisms underling overeating and other addictions.

68. STIMULATION OF DORSAL STRIATAL D2 RECEPTORS ATTENUATES THE κ-OPIOID-MEDIATED LOCOMOTION OF PREWEANLING RATS. Charntikov, S.; Herbert, M.S.; Halladay, L.R.; Marquez, E.M.; McDougall, S.A. Dept. of Psychology. California State University, San Bernardino, CA 92407 USA. Stimulation of κ-opioid receptors in the substantia nigra pars reticulata (SNPR) increases the locomotion of young rats: an effect blocked by systemic administration of a dopamine D2 receptor agonist. Based on these findings, we proposed that: (a) D2 receptors in the dorsal striatum are responsible for attenuating κ-opioid-induced locomotion, and (b) the effects of D2 receptor stimulation are mediated by the indirect pathway, which extends from the striatum to the SNPR via the globus pallidus (GP) and subthalamic nucleus (STN). To test the first hypothesis, rats were given an ip injection of saline or the κ-opioid agonist U50,488 on PD 18. After 20 min, rats received bilateral infusions of vehicle or the D2 receptor agonist NPA into the striatum, and the ability of NPA to block U50,488-induced locomotion was determined. To test the second hypothesis, rats were given sham or bilateral lesions of the GP or STN on PD 16. Two days later, saline- and U50,488-induced locomotion was measured after ip administration of vehicle or NPA. As predicted, striatal infusions of NPA attenuated the U50,488-induced locomotion of young rats. Contrary to our expectations, bilateral lesions of the GP or STN did not impair NPA's ability to block U50,488-induced locomotion. When considered together, these results suggest that: (a) stimulation of D2 receptors in the dorsal striatum is sufficient to attenuate the κ-opioid-mediated locomotion of young rats; and (b) the indirect pathway does not mediate the effects of striatal D2 receptor stimulation in this behavioral model. [Supported by NIH grant GM073842]

69. INVOLVEMENT OF THE ORBITOFRONTAL CORTEX IN CONTEXT-INDUCED AND COCAINE-PRIMED REINSTATEMENT OF COCAINE-SEEKING BEHAVIOR IN RATS. Lasseter, H.C.; Traina, S.A.; Fuchs, R.A. Dept. of Psychology. University of North Carolina, Chapel Hill, NC 27599 USA. Orbitofrontal cortex (OFC) damage produces impaired decision-making, impulsivity, and perseveration of maladaptive behaviors and potentially contributes to compulsive drug seeking in cocaine users. In a rat model of drug relapse, lateral OFC (lOFC) lesions, but not temporary functional inactivation of the lOFC, potentiate reinstatement of cocaine seeking following a cocaine priming injection (Fuchs et al., 2004). Interestingly, lOFC lesions fail to enhance reinstatement elicited by a response-contingent conditioned stimulus (CS). To further explore this phenomenon, rats with bilateral NMDA or sham lOFC lesions were trained to lever press for intravenous cocaine infusions in a distinct environmental context followed by extinction training in a different context. We assessed the effects of the lesions on reinstatement of cocaine-seeking behavior elicited by the cocaine-associated context as well as by a cocaine priming injection given before exposure to the extinction context. While lOFC lesions did not alter cocaine self-administration, they potentiated cocaine seeking following exposure to the cocaine-associated context and caused a perseveration in cocaine seeking following a cocaine priming injection. These results suggest the lOFC plays a different role in explicit CS-induced, context-induced and cocaine-primed cocaine-seeking behavior. To identify critical neuroadaptations that may underlie this effect, we are assessing the expression of the plasticity-associated gene, zif268, in elements of the brain relapse circuitry, including the nucleus accumbens and amygdala.

70. INVOLVEMENT OF LIMBIC BASAL GANGLIA IN ALCOHOL WITHDRAWAL. Buck, K.; Chen, G. Dept. Behavioral Neuroscience, Oregon Health & Science Univ., VAMC, Portland, OR 97239 USA. Physiological dependence and associated withdrawal can constitute a motivational force that sustains alcohol abuse. Although no animal model duplicates alcoholism, models for specific factors like the withdrawal syndrome are useful to identify potential genetic and neural determinants of liability in humans. We developed congenic mice that confirm a locus on chromosome 4 with a large effect on alcohol withdrawal. Using c-Fos expression as a high-resolution marker of neuronal activation, congenic mice showed significantly less neuronal activity associated with withdrawal than background strain mice in the substantia nigra reticulata (SNr), subthalamic nucleus (STN), and rostromedial lateral globus pallidus. Neural activation in subregions associated with limbic function was more intense than in subregions associated with sensorimotor function. Bilateral lesions of caudolateral SNr attenuated withdrawal, while lesions restricted to rostrolateral SNr or STN did not affect withdrawal convulsions. Caudolateral SNr lesions did not affect PTZ-enhanced convulsions. Our results suggest that this locus impacts withdrawal via basal ganglia circuitry associated with limbic function, and that the caudolateral SNr plays a crucial role. Given evidence that a gene(s) in the syntenic region of chromosome 9p influences alcoholism, our results inform human research on alcohol dependence and withdrawal. [AA011114, AA10760, VA]

71. CANNABINOID MODULATION OF HAMSTER CIRCADIAN ACTIVITY RHYTHMS. Gannon, R.L.; Sanford, A.M.; Castillo, E. Dept. of Biology. Valdosta State University, Valdosta, GA 31602 The master pacemaker generating endogenous circadian timekeeping rhythms is located in the suprachiasmatic nucleus (SCN) at the base of the hypothalamus. The pacemaker is entrained to environmental lighting conditions by afferent information conveyed by the optic nerve from the retina to the SCN, and this input is used to advance and delay the timing of the pacemaker each day at dawn and dusk, respectively. The ability of light to modulate phase advances of the pacemaker can be modulated by a variety of transmitter types, but to date the ability of cannabinoids to modulate circadian entrainment has not been reported. In this study we report that light-induced phase advances of hamster wheel running activity rhythms is inhibited by the cannabinoid receptor type 1 (CB1) agonist CP565940. Male Syrian hamsters kept in conditions of constant darkness for ten days with access to running wheels were exposed to a brief, 10 minute, 20 lux light pulse seven hours after their onset of running activity. This light pulse phase advanced the rhythm by 1.6 ± 0.1 hrs (mean ± SEM), and CP55940 (0.25 – 1 mg/kg) dose-dependently inhibited the effects of light when injected i.p 45 min before the light pulse, with a shift of only 0.2 ± 0.1 hrs with 1 mg CP55940. The inhibitory activity of 0.25 mg/kg CP55940 was partially antagonized by 0.5 mg/kg LY320135 while 0.125 mg/kg CP55940 was fully antagonized by 1 mg/kg AM251. Antagonists had no effect by themselves. Immunohistochemical studies using goat-anti CB1 antibodies identified significant densities of CB1 receptors in the hamster brain, including components of the circadian system such as the SCN, raphe nuclei, and intergeniculate leaflet of the thalamus. Supported by NSF IOB 0549980 (RLG).

72. EFFECTS OF REWARDING AND NON-REWARDING DRUGS ON SOCIAL REWARD CONDITIONED PLACE PREFERENCE. Thiel, K.J.; Dickey, E.D.; Okun, A.; Routt, V.; Neisewander, J.L. Dept. of Psychology. Arizona State University, Tempe, AZ 85287 USA. Drug and social rewards are particularly salient during adolescence. We have previously demonstrated that a low dose of cocaine interacts with social reward to produce an enhanced conditioned place preference (CPP) relative to the cocaine or social reward given alone. The present study further examined the nature of this drug:social reward interaction in adolescent male rats using another rewarding drug, nicotine, and a non-rewarding drug, dextromethorphan. First, we conducted a dose-response CPP experiment (0, .01, .03, .06 mg/kg) and selected a dose of 0.3 mg/kg, IV to establish CPP in the subsequent experiment because it was the lowest dose to support CPP. Rats were then assigned to one of four groups that received the following paired with their initially non-preferred side of the CPP apparatus: 1) saline + placement alone (Control); 2) nicotine + placement alone (Nicotine Only); 3) saline + placement with a partner (Social Only); 4) nicotine + placement with a partner (Nicotine/Social). The latter experiment was then replicated using dextromethorphan (30 mg/kg, IP) instead of nicotine. The results suggest there is a strong trend toward an interaction between nicotine and social context such that nicotine enhances social reward ($p=0.06$). In contrast, although dextromethorphan produced decreases in play behavior and locomotor activity, it failed to have an effect on social reward CPP. We conclude that the enhancement of social reward-CPP is specific to drugs that are rewarding. Supported by DA11064 and F31DA02746

73. INTRANIGRAL ADMINISTRATION OF A MODULATOR OF ENDOCANNABINOID FUNCTION (AM404) MODIFIES KAINIC ACID-INDUCED MOTOR SEIZURES. Mejía-Toiber, J.2 , García-Martínez, C.1, Romero-Cano, D. 2, Mendoza M.S., and Giordano M. 2; 1Dept. of Medicine, Universidad Autónoma de Aguascalientes 2 Instituto de Neurobiología-UNAM, Juriquilla, Querétaro 76230 Mexico. Within the past ten years, information about the endogenous cannabinoid system has been obtained, and interest in its possible role in the treatment of neurological disorders has been rising. In this study the effect of intranigral administration of AM404 on kainic acid (KA)-induced motor seizures was evaluated. AM404 is a modulator of anandamide (AEA) function, that enhances AEA availability by blocking its reuptake and inhibiting fatty acid amidohydrolase (FAAH), its degradative enzyme. Ten-male S-D rats (250-300 g) were implanted with cannulae directed to the left lateral ventricle, and bilateral cannulae to the substantia nigra pars reticulata (SNr). AM404 (10∝g/ml; Tocris, Ellisville MO) was administered into the SNr prior to intraventricular delivery of KA (3 nmol/3∝l). Animals were monitored for the following four hours by visual observation, seizures were rated according to Racine's scale. Seven days later, locomotor behavior was evaluated using an automated system (AccuScan Electronics, Columbus OH). Afterwards, animals were perfused and the location of the cannulae was evaluated; only data from animals with correct location of the cannulae were included in the behavioral analysis. The results showed that animals treated with AM404 showed less seizures type I-V than animals treated with vehicle; spontaneous locomotor activity was increased during the dark phase only in animals treated with vehicle. These preliminary results indicate that enhancing anandamide function within the SNr prevents KA-induced motor seizures, as well as long-term behavioral effects of KA treatment. Further studies are necessary to ascertain that these effects are mediated through the endocannabinoid receptor.

74. BEHAVIORAL EFFECTS OF METHAMPHETAMINE TOXICITY ARE TIME AND MOUSE STRAIN SPECIFIC. Phillips, C.; Rhoades, R.; Hodges, A.B.; Krasnova,I.N.; Cadet, J.L.; Hohmann, C.F. Department of Biology, Morgan State University and Molecular Neuropsychiatry Branch, National Institute on Drug Abuse, NIH/DHHS Baltimore, MD. Methamphetamine (METH) is a toxic psychostimulant that causes neuronal damage in mammalian brains. Previous studies in our labs have investigated short- and long-term effects of neurotoxic METH doses on cognitive behaviors in male Balb/CByJ mice. We found significant learning and memory deficits 10 days after METH administration (i.p., 7.5 mg/kg x 4 times, every 2 hours) compared to control that was followed by gradual cognitive recovery over the next five months. In contrast, locomotion in the METH-treated mice was normal at 10 days after injections but significantly decreased by five months post-drug. In the present study, we investigated the effects of METH toxicity on mice of the ICR strain, following the same injection protocol as described above. To assess behavioral performance, mice were tested on an Open Field Object Recognition (OFOR) task, which allows the examination of locomotion, exploratory activity, spatial memory and novelty response at 2 week, 3 month and 5 month intervals following the injections. ICR mice had normal locomotion at 2 weeks after METH administration but, in contrast to Balb/C, significantly decreased exploratory activity. Similar to METH-treated Balb/C mice, ICR animals showed reduced response to object displacement, suggesting deficit in spatial memory. However, ICR mice also responded with decreased exploration to object novelty suggesting neophobia. We are currently analyzing behavioral performance at 3 and 5 months time-points to compare the differential locomotor and cognitive response to neurotoxic METH treatment between two strains of mice. Supported by: SO6 GM051971 and R25 GM058904 to C.F.H.

75. CHANGE IN SENSITIVITY TO INTRA-HIPPOCAMPAL MICROINJECTION OF FINASTERIDE VS ALLOPREGNANOLONE ON SEIZURE SUSCEPTIBILTY DURING ALCOHOL WITHDRAWAL. M.A. Tanchuck, K.R. Gililland, C. Snelling, G.P. Mark, D.A. Finn. VAMC Research & Dept. of Behavioral Neuroscience, OHSU, Portland, OR 97239. The neurosteroid allopregnanolone (ALLO) is a positive modulator of GABAA receptors that can modulate ethanol (EtOH) withdrawal. Finasteride (FIN) inhibits ALLO production and has been found to reduce some of the effects of EtOH. The present studies determined whether manipulation of the neurosteroid levels in the hippocampus would alter seizure susceptibility. The purpose of this study was to administer ALLO or FIN via microinjection and determine whether sensitivity was altered during ethanol withdrawal. During withdrawal, Withdrawal Seizure Prone (WSP) mice were tolerant to the anticonvulsant effect of intra-hippocampal ALLO infusion, measured by seizure susceptibility to the convulsant pentylenetetrazol, consistent with systemic injection. Finally, intra-hippocampal FIN during the development of physical dependence significantly increased alcohol withdrawal severity, measured by handling-induced convulsions. These findings are the first demonstration that bi-directional manipulation of hippocampal ALLO levels during alcohol withdrawal rendered WSP mice less sensitive to ALLO's anticonvulsant effect and more sensitive to FIN's proconvulsant effect, suggesting an alteration in the sensitivity of hippocampal GABAA receptors to fluctuations in GABAergic neurosteroids during ethanol withdrawal.

76. VOCAL AND LOCOMOTOR RESPONSES TO AMPHETAMINE IN THE INBRED LONG-EVANS RATS. Brudzynski, S.M.; Duffus, S.; Gibson, B.; Burgdorf©ö, J., Dept. of Psychology, Brock University, St. Catharines, ON, L2S 3A1 Canada, ©ö- Dept. of Biomedical Engineering, Northwestern University, Evanston, IL, USA. Three lines of inbred Long-Evans rats were developed, based on the number of 50-kHz calls emitted during heterospecific play (¡°tickling¡±) at 24-25 days of age. High line and Low line contained animals emitting high and low levels of 50 kHz calls, respectively. The non-selected Random line served as a control. The goal of the study was to test the hypothesis that adult rats in these three lines (at the 20th generation) will differ in their responsiveness to intracerebral, as well as systemic amphetamine. After intracerebral application of 10 ¥ìg of amphetamine into the nucleus accumbens, the number of 50 kHz calls was recorded for 5 min. After systemic injection of the drug (1.5 mg/kg i.p.), locomotor activity was measured in the Digiscan activity cage for 20 min. Overall, the intraaccumbens application of amphetamine almost doubled the number of emitted 50 kHz calls ($p < 0.01$). There were, however, significant differences in responses among the lines. Rats in the Random and High lines significantly increased the number of 50 kHz calls ($p < 0.05 - 0.001$) as compared to saline control, while the rats of the Low line did not show any significant increase. Systemic application of amphetamine showed a congruent pattern. Overall, systemic amphetamine significantly increased locomotor activity as compared to that after saline ($p < 0.0001$). Rats in the Random and High lines, but not in the Low line, significantly increased locomotor activity after amphetamine ($p < 0.01$). Locomotor activity of rats in the Low line was not significantly higher than that after saline. Supported by ISAN.

77. STIMULATION OF 5-HT1B RECEPTORS ENHANCES COCAINE REINFORCEMENT YET REDUCES COCAINE-SEEKING BEHAVIOR. Pentkowski, N.S.; Browning, J.; Acosta J.I.; Hamilton, L.; Duke, F.; Neisewander, J.L. Department of Psychology, Arizona State University, Phoenix AZ 85287 USA. Paradoxically, stimulation of 5-HT1B receptors enhances cocaine reinforcement but attenuates reinstatement of extinguished cocaine-seeking behavior produced either by cocaine priming or cocaine-associated cues. We revisited this issue by examining effects of a 5-HT1B agonist, CP 94,253, on cocaine-primed reinstatement using a low priming dose to increase sensitivity for detecting a predicted enhancement of cocaine-seeking behavior. Rats were trained to self-administer cocaine (0.75 mg/kg, IV) paired with light and tone cues. They then underwent daily extinction training to reduce cocaine-seeking behavior (operant responses without cocaine reinforcement). Next, rats were tested with CP 94,253 pretreatment (3-10 mg/kg, IP) and cocaine priming (10 or 2.5 mg/kg, IP). Responses during reinstatement tests produced no consequences. Cocaine dose-dependently reinstated cocaine-seeking behavior, but contrary to our prediction, CP 94,253 reduced the reinstatement effect of both priming doses. We next examined effects of CP 94,253 (5.6 mg/kg) on cocaine self-administration across a range of cocaine doses (0-1.5 mg/kg, IV). Rats were tested twice at each dose, receiving vehicle prior to one test and CP 94,253 prior to the other, with order counterbalanced. Additional sessions with the training dose were given between tests to return to baseline. The results demonstrated that CP 94,253 shifted the cocaine dose-effect curve leftward, consistent with enhanced reinforcement. When saline was substituted for cocaine, CP 94,253 reduced response rates (i.e., cocaine-seeking behavior), suggesting that incentive motivational effects of cocaine-paired cues were reduced. The results continue to be consistent with previous research suggesting that stimulation of 5-HT1B receptors increases cocaine reinforcement yet decreases motivation for cocaine produced by cues or cocaine priming. (DA11064, Ford Foundation, and APA Diversity Program in Neuroscience)

78. INTERACTIVE EFFECTS OF GENE KNOCKOUT OF THE SEROTONIN 1A AND 1B RECEPTORS WITH GENE KNOCKOUT OF THE DOPAMINE TRANSPORTER ON COCAINE CONDITIONED PLACE PREFERENCE. Hall, F.S. (1); Perona, M.T.G. (1); Sora, I. (2); Tecott, L.H. (3); Hen, R. (4); Uhl, G.R. (1) (1) Molec. Neurobiol. Branch, NIDA-IRP/NIH/DHHS, Baltimore, MD; (2) Dept. Neurosci., Tohoku Univ. Grad. Sch. Med., Sendai, Japan; (3) Dept. Psychiatry, UCSF, San Francisco, CA; (4) Center for Nurobiology and Behavior, Columbia Univ., New York, NY Investigations into the mechanisms of cocaine reward have revealed the importance of both the serotonin (SERT) and dopamine (DAT) transporters. Combined knockout of the DAT and SERT genes completely blocks cocaine conditioned place preference. Several serotonin receptor subtypes may be involved in these effects, including the serotonin 1A receptor (5-HTR1A) and the serotonin 1B receptor (5-HTR1B). To further explore the necessary dopamine-serotonin interactions for cocaine reward, combined transporter/receptor gene deletions were studied, including combined DAT/5-HTR1A, DAT/5-HTR1B, and DAT/5-HT1A/5-HT1B knockout mice. All double mutants were viable, but triple knockout mice (DAT -/- 5-HT1A -/- 5-HT1B -/-) were observed in proportions far less than expected. In contrast to previous studies, in these DAT knockout strains, DAT alone was found to reduce the rewarding effects of cocaine in the conditioned place preference paradigm. Interestingly, gene knockout of 5-HT1A or 5-HT1B were found to fully restore the rewarding effects of cocaine, which may indicate that the observation of effects of DAT is dependent on the level of expression of these genes. By contrast, combined deletion of both serotonin receptor genes in DAT -/- 5-HT1A -/- 5-HT1B +/- or DAT -/- 5-HT1A +/- 5-HT1B -/- completely eliminated the rewarding effects of cocaine, similar to that observed in DAT/SERT double knockout mice. These data re-emphasize the importance of both serotonin and dopamine system genes in cocaine reward, as well as the polygenic nature of drug reward.(Support: NIDA-IRP/NIH/DHHS)

79. ALLOPREGNANOLONE AND PROGESTERONE LEVELS DURING ETOH WITNDRAWAL IN ADRENALECTOMIZED AND GONADECTOMIZED DBA2/J MALE AND FEMALE MICE. Gililland, KR; Tanchuck, MA; Finn, DA OHSU Dept. of Behavioral Neuroscience and Dept. of Veterans Affairs, Portland, OR 97239. Previous research has shown that ethanol (EtOH) administration in rodents causes a considerable rise in neuroactive steroid (NAS) concentrations in both the blood and brain. Further research has shown that this increase is due to synthesis in the peripheral sources of NAS, namely the gonads and the adrenal glands. Recent work in our lab and others has shown that inhibiting the rise in NAS seen to EtOH exposure (through either surgical or pharmaceutical manipulations) can inhibit behavioral effects of both EtOH intoxication and withdrawal. Removal of the adrenals (ADX)and gonads (GDX) increased the severity of withdrawal from a 4 g/kg dose of EtOH, and this difference was not due to changes in EtOH metabolism. The current experiments begin to investigate the mechanism(s) underlying the effects of NAS inhibition on withdrawal severity. As allopregnanolone (ALLO) is the most potent of the NAS at GABAA receptors, levels of ALLO and its precursor, progesterone were measured in brain or blood, respectively, in ADX/GDX or SHAM animals that were scored for withdrawal or were undisturbed. The pattern of the results give insight to the underlying mechanism(s) causing increases in withdrawal severity when NAS sources are removed. Supported By: AA10760, AA12439, 5T32-AA07468, the N.L. Tarter Foundation and the Dept. of Veterans Affairs.

80. EFFECT OF SYSTEMIC AND INTRA-TEGMENTAL METHAMPHETAMINE ON ACETYLCHOLINE AND DOPAMINE LEVELS IN THE VENTRAL TEGMENTAL AREA IN THE MOUSE. Dobbs, L. & Mark, G.P.: Dept. of Behavioral Neuroscience. Oregon Health & Science University, Portland, OR 97239 USA. Acetylcholine (ACh) is an important mediator of dopamine release and the reinforcing characteristics of drugs of abuse in the mesocorticolimbic pathway. However, the effects of methamphetamine (MA) on ventral tegmental area (VTA) ACh and dopamine release remain poorly characterized. The present study used microdialysis to measure extracellular ACh and dopamine in the VTA following systemic and intra-VTA administration of methamphetamine. Male C57BL/6J mice received an intraperitoneal injection (saline, 5 mg/kg or 2 mg/kg) and intra-VTA infusion (vehicle, 1 mM or 100 ìM) of MA and dialysate samples were alternately analyzed for ACh and dopamine content. Locally perfused methamphetamine (1 mM) significantly increased somatodendritic dopamine output to 2473% of baseline during the 20 minute drug perfusion. Systemic methamphetamine (5 mg/kg) significantly increased somatodendritic dopamine to 941% of baseline during the first 20 minutes post injection. There was a 297% and 1240% increase in dopamine following the 2 mg/kg and 100 ìM doses of methamphetamine, respectively. Systemic methamphetamine significantly increased ACh levels to 275% of baseline for 40 – 60 minutes (2 mg/kg) and up to 397% of baseline for 40 -160 minutes (5 mg/kg) after injection. ACh remained elevated above baseline for 2 to 5 hours post injection, depending on the MA dose. Conversely, there was no change in ACh levels following either intra-VTA MA at either dose. These data suggest that MA acts in the VTA to induce a robust and short-lived increase in somatodendritic dopamine release but acts in an area upstream from the VTA to produce a prolonged increase in ACh release in the VTA.

81. NEURAL CIRCUITRY OF MEMORY RECONSOLIDATION PROCESSES THAT FACILITATE CONTEXT-INDUCED COCAINE SEEKING. Ramirez, D.R.; Xie, X.; Bell, G.H.; Eaddy, J.L.; Fuchs, R.A. Dept. Psychology, University of North Carolina, Chapel Hill, USA. The basolateral amygdala (BLA), dorsal hippocampus (DH), dorsolateral caudate-putamen, and dorsomedial prefrontal cortex are critical for the expression of context-induced cocaine seeking, and the same brain regions may also play a role in context-cocaine memory reconsolidation processes that foster this behavior. To test this hypothesis, rats were trained to lever press for un-signaled cocaine infusions in a distinct context then received extinction training in a different context for 7 days (EXT-CTX). Rats were then re-exposed to the cocaine context for 15 min to reactivate context-cocaine associations. After this session, when memory reconsolidation was expected to occur, rats received intra-cranial anisomycin (ANI), a protein synthesis inhibitor, or tetrodotoxin (TTX), a sodium channel blocker, treatment into one of the above brain regions. After minimum 2 additional sessions in the EXT-CTX, we assessed the effects of these manipulations on cocaine seeking in the cocaine context. ANI administered into the BLA or TTX administered into the DH or BLA following the memory reactivation session subsequently inhibited context-induced cocaine seeking, whereas all other manipulations failed to alter cocaine seeking. These effects were dependent on memory reactivation and were not observed if ANI or TTX was administered into a control brain region just dorsal relative to the BLA or DH. These findings implicate the BLA in post-reactivation stabilization, and the DH in post-reactivation processing, of context-cocaine memories that maintain context-induced cocaine seeking.

82. ARGON PREVENTS AMPHETAMINE SENSITIZATION. David, H.N.; Dhilly, M.; Poisnel, G.; Debruyne, D.; Abraini, J.H. UMR CI-NAPS 6232, Université de Caen, CNRS, CEA, Centre CYCERON, BP 5229 Boulevard Becquerel, 14074 Caen Cedex, France Repeated exposure to amphetamine produces behavioural sensitization, which is characterized by an augmented locomotor response to a subsequent amphetamine challenge. Dopaminergic and glutamtergic neurotransmissions have been showed to play a critical role. The opioid system arise interest due to the collective role of the opioidergic and dopaminergic systems in the regulation of locomotor and motivational behaviours. In the present study, we have investigated the potential neuroprotective effects of the inert gas argon on the behavioural sensitization and on the alterations of µ receptors induced by amphetamine. We demonstrate that Argon prevents behavioural sensitization. Furthermore, our results show that amphetamine induces an increase of the activity of the opioidergic system that is prevented by argon.

83. PREFRONTAL AND AMYGDALOID CONTROL OF THE EXPRESSION OF BEHAVIOURAL SENSITIZATION TO AMPHETAMINE. Degoulet M., Rouillon C, David HN, Rostain JC, Abraini J.H. UMR CI-NAPS 6232, University of Caen, CNRS, CEA. Centre CYCERON, 14074 Caen, FRANCE Beyond the well-establish of the nucleus accumbens (NAcc) in the expression of behavioural sensitization to amphetamine, the role of the prefrontal cortex (mPFC) and the basolateral amygdala (BLA), which both send glutamatergic projections to the NAcc, have been poorly examined. In the present study, we investigated how lidocaine infused in the mPFC or the BLA modulated behavioural locomotor sensitization induced by repeated administration of systemic amphetamine. Rats well habituated to their environmental conditions and experimental protocol were given repeated administration of systemic amphetamine. Once behavioural sensitization was developed, rats were challenge with amphetamine and infused with saline (control) or lidocaine into the mPFC or the BLA. We found that reversible inhibition by lidocaine of the mPFC, or the BLA, blocks the expression of behavioural sensitization to amphetamine, while control animals do express sensitization. Our results bring new insight on the role of the mPFC and the BLA in the expression of behavioural sensitization to amphetamine, indicated that, in individuals well habituated to the drug-associated context, both the mPFC and the BLA would play a key role. This suggests that the expression of behavioural sensitization to amphetamine is not only dependent upon the NAcc but also involved a circuit that drives the expression of context –dependent addictive behaviours. Our results further provide good experimental evidences for human imaging studies that have demonstrated significant brain activation patterns in the prefrontal cortex and amygdala in addicts exposed to drug-related cues.

84. SUBTYPE-SPECIFIC CHARACTERIZATION OF THE EFFECTS OF POST-RETRIEVAL BETA-ADRENOCEPTOR ANTAGONISM IN A COCAINE CONDITIONED PLACE PREFERENCE PARADIGM. Bernardi, R.E.[1]; Lattal, K.M.[1]; Berger, S.P.[12] [1]Dept of Behavioral Neuroscience, Oregon Health Sci. Univ., Portland, OR, USA. [2]Dept of Psychiatry, Portland VA Med. Ctr., Portland, OR, USA. Previous work from our laboratory has shown that in a cocaine conditioned place preference paradigm, post-test administration of the non-specific beta-adrenergic antagonist propranolol (10 mg/kg i.p.), but not vehicle, disrupts preference on a subsequent test (Bernardi et al., 2006). Since then, other laboratories have also shown an effect of post-retrieval propranolol in drug-related learning paradigms. The current study examined the subtype specificity of the post-retrieval effects of beta-adrenoceptor antagonism in the cocaine conditioned place preference paradigm. In two separate studies, 24 hr following cocaine conditioning, rats were given a drug-free test of conditioned place preference, followed immediately by administration of the beta1 antagonist Betaxolol (0, 5, or 10 mg/kg i.p.) or the beta2 antagonist ICI 118,551 (0 or 8 mg/kg i.p.). Consistent with our previous work showing disruption of place preference following post-retrieval propranolol, rats receiving ICI 118,551-- but not Betaxolol-- following the first preference test showed no preference for the cocaine-paired floor during a second test of place preference 24 hr later, while vehicle-treated rats continued to express a preference for the cocaine-paired floor. This suggests that post-retrieval effects of beta-adrenergic antagonism on drug cue-induced behaviors are likely mediated by the beta2- and not the beta1-adrenergic receptor.

85. ALCOHOL AFFECTS PHARMACOKINETICS AND PHARMACODYNAMICS OF MDMA Jones, B.C.1; Ben-Hamida, S.2; Pereira de Vasconcelos, A.2; Jackisch, R.3, Cassel, J.C.2 1Department of Biobehavioral Health, Penn State University, University Park PA 16802 2LINC, UMR 7191 CNRS Université Louis Pasteur, 12 rue Goethe F-67000 Strasbourg, France. 3Institut für Experimentelle und Klinische Pharmakologie der Universtät Freiburg, Hansastrasse 9A, D79104 Freiburg, Germany For the past few years, we have been studying the interaction between alcohol (EtOH) and Ecstasy (MDMA). To date and in rats, we have shown that EtOH taken together with MDMA causes a synergestic increase in locomotor activity (vs. MDMA), alters the thermoregulatory disruption caused by MDMA, shows a pattern of sensitization unique to MDMA (vs. cocaine, amphetamine) and a tolerance (or depending on dosing schedule, sensitization) to thermoregulatory effects unrelated to previous exposure to EtOH or MDMA. As concerns the behavioral effects of the combination, we hypothesized that EtOH increases activity of MDMA in dopamine reward pathways and may also affect the distribution and disappearance of MDMA in the brain. In our most recent efforts, we now show that in rats, EtOH + MDMA enhances metabolic activity particularly in the ventral striatum (by 2DG imaging) and shifts evoked neurotransmitter release in striatal slices from serotonin to dopamine vs MDMA alone. Combination of both drugs also increases distribution of MDMA to the brain and shifts conditioned place preference from no evident preference for MDMA or EtOH alone, to marked preference when the two drugs are combined. These results raise the issue that EtOH may increase the liability for compulsive use/abuse of MDMA and that the increased tissue concentrations of MDMA in the presence of EtOH may increase the risk for tissue damage.

86. CHRONIC PHYSICAL ACTIVITY IN RODENTS INCREASES MU-OPIOID RECEPTOR BINDING. Lawrence, RC; Junor, L; Ford, KA; Wilson, MA. Department of Psychology, University of South Carolina, and Department of Pharmacology, Physiology & Neuroscience, University of South Carolina School of Medicine, Columbia SC 29208 Chronic physical activity has been shown in both humans and rodents to alter behavior and neurochemistry. Importantly, chronic voluntary physical activity produces alterations in opioid receptor-mediated behaviors and is associated with alterations in opioid receptor sensitivity. To determine if behavioral effects of physical activity are due to alterations in opioid receptors, mu opioid receptor (MOR) binding in chronic wheel running and sedentary rats was compared. Male Sprague Dawley rats were given free access to a running wheel for 8 weeks (WR, n=5) or housed in a similar cage with a locked wheel (LC, n=5). After 8 weeks, animals were euthanized and brains frozen on dry ice for analysis of mu opioid receptor binding. Sections were cut at 16 microns, and anatomic localization was determined via acetylcholinesterase staining on adjacent slides. Mu opioid receptor expression was assessed in thalamus, hippocampus, striatum, amygdala, ventral medial hypothalamus, preoptic area, lateral hypothalamus, paraventricular nucleus of the hypothalamus (PVN), nucleus accumbens, and the bed nucleus of the stria terminalis (BNST) using autoradiographic 3H-DAMGO binding analysis (5nM). Chronic wheel running (8 weeks) produced significant increases in mu opioid receptor expression in nucleus accumbens and BNST compared to locked control groups, although several other regions showed trends toward increased levels of mu opioid receptor binding that were not statistically significant. Changes in BNST may be related to anxiety-related changes induced by chronic physical activity, while those in nucleus accumbens may associated with the rewarding aspects of voluntary wheel running in rodents. Supported by NIH RO1 MH063344 to MAW

87. EFFECTS OF DECREASING AMYGDALAR MU OPIOID RECEPTORS ON ANXIETY RESPONSES. Wilson, MA; Ford, KA; Smith, LA; Zhang, J; Wilson, SP. Dept. Pharmacology, Physiology & Neuroscience, Univ. South Carolina School of Medicine, Columbia SC. Our work suggests that opioid peptides acting via mu opioid receptors (MOR) in the central amygdala differentially influence behaviors in two models of unconditioned anxiety. The present studies further investigated the role of MOR in anxiety-related behaviors using virus-mediated gene transfer to diminish expression of MOR in the amygdala. Anxiety was assessed in two animal models of anxiety behavior, the elevated plus maze and the defensive burying task. Since opioid peptides in the amygdala modulate nociception, defensive burying was elicited using a predator (ferret) odor. We developed lentiviral vectors expressing a full length MOR antisense sequence and several miRNA sequences directed against MOR under control of the synapsin promoter. The effectiveness of antisense sequences f were tested in 293T cells transiently expressing the cDNAs for MOR or DOR. Such studies demonstrated that these sequences decreased MOR expression by ~70%, but did not alter DOR expression. The MOR antisense lentiviral vector also decreased MOR expression in the amygdala as analyzed using in situ hybridization for mRNA, radioimmunocytochemistry, and 3H-DAMGO binding; the miRNA-expressing vectors are currently being tested in vivo. For behavioral analysis, rats were injected with the Antisense-MOR or control virus bilaterally into amygdala. Ten days later animals were tested in the plus maze, followed by the defensive burying test two days later. The animals with Antisense-MOR showed no changes in open arm time in the plus maze, but significantly more defensive burying. Thus, MOR may more directly modulate defensive burying, since both injection of the MOR agonist into amygdala and decreases in MOR expression using viral vectors shifted burying behavior. Supported by NIH RO1 MH063344 to MAW.

88. PRENATAL EXPOSURE TO ALCOHOL/NICOTINE ALTERS OXYTOCIN RECEPTOR BINDING BUT NOT mRNA IN ADULT RATS. Cox E.T.; Williams S.K.; McMurray M.S.; Jarrett T.M.; Fay E.E.; Overstreet D.H.; Johns J.M. Departments of Neurobiology, Psychology and Psychiatry, UNC-Chapel Hill Chapel Hill, NC 27599. Prenatal exposure to alcohol or nicotine alone is known to be detrimental to human and animal newborns but few studies exist on the effects of exposure to nicotine and alcohol combined. We have reported that behavior and oxytocin levels are altered in adolescent and adult rat offspring prenatally exposed to alcohol/nicotine or cocaine. This study was designed to determine if prenatal exposure to alcohol and nicotine impact oxytocin protein (mRNA) or receptor binding in adult rats in brain regions associated with behavior. Pregnant Sprague-Dawley rats were given either a control or alcohol (35% caloric intake from ethanol) liquid diet and approximately 5mg/kg/day of nicotine (osmotic pump implant) on gestational days (GD) 5 through 20. Pups were reared by their biological mother and killed on PND 60. Their brains were sliced for oxytocin mRNA and receptor binding assessment using in situ hybridization and autoradiography respectively. There were no differences in oxytocin message in any brain region tested. There were region specific effects of gender and prenatal exposure condition on oxytocin binding levels in the Nucleus Accumbens, Ventral Tegmental Area, and Ventral Medial Hypothalamus. Results indicate oxytocin receptor changes in brain regions associated with reward and motivation, in a prenatal exposure model associated with increased alcohol consumption. These and other findings implicate oxytocin as perhaps having a role in drug related behaviors. The study was supported by a pilot project (to Dr. J.Johns) from NIH 5 P60 AA11605-10 (awarded to Dr. F. Crews).

89. PRENATAL EXPOSURE TO ALCOHOL/NICOTINE AFFECTS ALCOHOL CONSUMPTION IN ADULT BUT NOT ADOLESCENT RATS. Williams, S.K.; McMurray, M.; Jarrett, T.M.; Cox, E.T.; Fay, E.; Overstreet, D.H.; Johns, J.M. Departments of Neurobiology, Psychology, Psychiatry UNC-Chapel Hill Chapel Hill, NC 27599 USA Nicotine and alcohol are often used concomitantly during pregnancy. Detrimental effects of prenatal exposure to either drug alone are well-established in human and animal models, but the outcomes following their combined usage are unclear. This study determined if prenatal exposure to combined alcohol and nicotine impacts alcohol preference/consumption during adolescence (postnatal days (PND) 30-45) and early adulthood (PND 60-75). Pregnant Sprague-Dawley rats were given a 35% alcohol-derived calorie or control liquid diet, and approximately 5mg/kg/day nicotine (through an osmotic pump) from gestational day (GD) 5-21. Pups were reared by their biological mothers. On PND 30, a two-bottle choice (2BC) saccharin (0.1%) preference test was given. Over PNDs 31-35 subjects were given a 2BC test between tap water or ascending ethanol concentrations (2, 4, 6, 8, and 10%), followed by 3 days of forced alcohol consumption (10%) and then 5 days of 2BC (water or 10% alcohol). An identical preference testing procedure was used for the same subjects starting on PND 60. Alcohol/nicotine exposed pups were smaller than controls from birth through PND 45. Although subjects exhibited minor differences in alcohol consumption during adolescence, there were significant differences in adult drinking patterns based on gender and prenatal exposure condition. These results suggest that prenatal exposure to alcohol/nicotine impacts drinking behavior dependent on test age. This study was supported by a pilot project (Dr. J. Johns) from NIH 5P60 AA11605-10 (awarded to Dr. F. Crews).

90. IN UTERO COCAINE EXPOSURE ALTERS PUP PRODUCED STIMULI RELEVANT TO MATERNAL CARE. McMurray, M.S.; Jarrett, T.M.; Moy, S.; Styner, M.; Johns, J.M. Departments of Psychology and Psychiatry. UNC, Chapel Hill, NC 27599 USA. Reported deficits in maternal care of cocaine-exposed rat pups suggest that pup-elicited cues may play a role in these deficits. It is well documented that rodent mothers attend to specific stimuli of pups such as vocalizations, body temperature, nursing elicitation through touch, and olfactory stimulus cues. Thus, in these preliminary studies, ultrasonic vocalizations and body temperatures of cocaine-exposed and untreated pups were examined on postnatal days 1 and 5. In addition, cocaine-treated and untreated dams were tested for behavioral preference of odors from pup urine of either cocaine-exposed or unexposed pups on an olfactory choice test. Potential neurobiological mechanisms were examined using structural magnetic resonance imaging (MRI). Results indicate that cocaine-exposed pups have altered cry patterns, similar to those of human infants with prenatal alcohol exposure and prenatal selective serotonergic reuptake inhibitor-exposure. Cocaine-exposed pups also demonstrate higher skin temperatures than untreated pups. All dams were found to spend more time in the vicinity of urine from untreated pups than cocaine-exposed pups, suggesting altered chemical components of cocaine-exposed pups. MRI revealed altered grey to white matter ratios in cocaine exposed pups, as well as volumetric differences in specific regions. Whether specific differences are correlated with altered maternal care of cocaine-exposed pups will be addressed in future studies and results may prove important for translational studies of maternal-infant dyads. This work was supported by NIH DA R01-13283 and DA R01-13362.

91. ANIMAL MODELS OF DEPRESSION AND ALCOHOLISM EXHIBIT REDUCED MATERNAL BEHAVIOR. Jarrett, T.M.[1,2]; Williams, S.K. [2]; Fay, E. E.[3]; McMurray, M.S.[4]; Overstreet, D.H. [5,6]; Johns. J.M. [2,4,5,6]. MD-PhD Program [1], Curriculum in Neurobiology [2], Department of Psychology [3], Behavioral Neuroscience Program [4], Bowles Center for Alcohol Studies [5], Department of Psychiatry [6]. The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 USA. Background: Maternal behavior is increasingly being recognized for its role in the development of many social behaviors including stress response and drug taking behaviors. Recognizing the level of maternal care typical in rat strains used as animal models of anxiety and substance abuse will assist in interpreting findings using these important preclinical models of human conditions. Methods: In this study ethanol-preferring Fawn-Hooded (n = 5) and P rat (n = 5) strains were compared to the non-ethanol preferring Sprague-Dawley (n = 9) strain. Females from each strain were mated within strain, and housed singly upon pregnancy determination. On postpartum day one dams were given a 30-minute habituation period alone in the testing chamber, followed by the return of pups. Maternal behavior was taped for 30 minutes. Tapes were scored by 2 independent observers. Eleven maternal behaviors were quantified for frequency, duration, and latency. Results: On key indices of maternal behavior, Fawn-Hooded rats performed significantly fewer maternal behaviors (lick pups and crouch) for significantly shorter periods of time (crouch) compared to the Sprague-Dawley rats. P-rats also performed significantly fewer maternal behaviors (crouching) for significantly shorter periods of time (crouching and touch/sniff pups) than the Sprague-Dawley strain. Conclusions: These results suggest that the depression-like symptoms and ethanol-preferring characteristics of the Fawn-Hood strain and ethanol-preferring trait of the P-rat strain could be associated with decreases in maternal behavior, though this has yet to be directly tested. This study was supported by a pilot project award to Dr. Johns out of the NIH Center Grant 5 P60 AA11605-10 awarded to Dr. Fulton Crews.

Stress, Anxiety, Fear and Defense

92. ADRENAL ACTIVATION RELATED TO THE WILD RUNNING BEHAVIOR IN THE RAT. Costa, M.M.; Pereira, P.C.; Hage, M.P.; Molico, E.; Miranda, T.; de Paula, H.M.G. Department of Biological Sciences, FC – UNESP / Brazil. Wild Running (WR) behavior is the violent running fit exhibited by sensitive rats in response to high-intense acoustic stimulation. Traditionally considered a pre-convulsive behavior, it has been studied as a panic-like reaction by our research group. Considering that defensive reactions (like panic and anxiety) selectively activate the adrenal glands, the aim of the present work was investigate some aspects of the adrenal activation associated with the WR manifestation. Wild runnings were induced in male Wistar adult rats by stimulations with a loud ringing bell (112dB) during 1 min. Initially, nine WR-sensitive (WR-s) and nine -resistant rats (WR-r) were compared regarding their corticosterone secretion and adrenal glands size in basal conditions. For that, previously tested animals were sacrificed, the trunk blood was collected for the serum corticosterone determination (RIA) and the adrenals were weighed. No differences were found. In a second step, WR-r (n=9) and WR-s (n=9) animals were submitted to the same procedures, but 30 seconds after an acoustic stimulation that evoked the WR behavior in the WR-s rats, but not in the WR-r. In such situation, corticosterone levels were lower ($p<0.05$) for the WR-s rats and adrenal weights were not statistically different between the groups. However, adrenals were heavier and glycemia increased ($p<0.05$) for both groups of rats after acoustic stimulation compared with the basal condition. These results are suggestive that WR is associated with adrenomedullar rather than adrenocortical activation, and this fits with the profile of a flight-or-fight reaction. Financial Support: FAPESP (06/56892-3).

93. DIFFERENCES IN OPEN-FIELD AND ELEVATED PLUS-MAZE BEHAVIOR BETWEEN WILD RUNNING-SENSITIVE AND WILD RUNNING-RESISTANT RATS. Pereira, P.C.; Hage, M.P.; Molico, E.; Costa, M.M.; Miranda, T.; de Paula, H.M.G. Department of Biological Sciences, FC – UNESP / Brazil. The open-field (OF) and the elevated plus-maze (EPM) are among the most common etho-experimental tests used for study the defensive behaviors of laboratory rodents. The Wild Running (WR) behavior observed in the audiogenic seizure paradigm closely resembles a panic manifestation related to flight reaction. Aiming to investigate the relationships between WR susceptibility and defensiveness in the rat, this work presents the results of WR-sensitive rats tested on the OF and on the EPM. Initially, common male Wistar rats were categorized as WR-sensitive (WR-s) or -resistant (WR-r) ones. For that, they were individually stimulated by a loud ringing bell (112 dB) for 60 s inside a sound-proof chamber. If the rat exhibited a clear episode of WR, the bell was switched off and it was classified as WR-s. The WR-r animals usually behaved very differently, remaining still, exploring or grooming during the trial. After a few days, they were exposed to the OF and to the EPM following conventional procedures. Data comparison between the groups showed statistically significant differences ($p<0.05$) regarding the less time spent by the WR-s rats in the central squares of the OF. In contrast, they spent more time in the open arms of the EPM and presented increased proportion of open arms entrances compared with the WR-r animals ($p<0.05$). Other variables from both tests, including locomotion indexes, were similar between the groups. We conclude that WR-s and WR-r rats differ in some aspects of defensive behaviors, with the apparent contradictory EPM behavior of WR-s probably due a more anxiogenic condition of this test. Financial Support: FAPESP (06/56892-3).

94. SOCIAL BUFFERING MITIGATES CONDITIONED FEAR RESPONSES WITHOUT PHYSICAL CONTACT IN MALE RATS. Kiyokawa, Y.; Takeuchi, Y.; Nishihara, M.; Mori, Y. Graduate School of Agricultural and Life Sciences. The University of Tokyo, Tokyo 113-8657 JAPAN. In a phenomenon known as gsocial buffering h in various species, stress responses are less distinct when animal are exposed to a stressor with one or more conspecific animals. We previously reported in adult Wistar male rats that social buffering mitigated conditioned fear responses (freezing and Fos expression in the paraventricular nucleus) to an auditory and contextual conditioned stimulus. However, there remains another possibility that these results were simply due to physical disturbance by another rat because the dyad was placed in the same box in these studies. To clarify this point, we investigated the role of physical contact between the dyad in this study. When fear-conditioned rats were exposed to an auditory conditioned stimulus solitary, they showed freezing and increased Fos expression in the paraventricular nucleus as compared to non-conditioned rats. These behavioral and neural responses were mitigated when a conspecific associate attended on the subject, regardless of its separation by a wire mesh or double wire meshes. However, social buffering effects were not observed if an acrylic board was placed between the double wire meshes partition or another species animal (guinea pig) was used as an associate with a wire mesh partition. These results suggest that social buffering mitigates conditioned fear responses without physical contact in male rats.

95. PERINATAL DIETARY PHYTOESTROGEN EXPOSURE ALTERS USV EXPRESSION DEPENDENT ON AGE, ENVIRONMENTAL TEMPERATURE, AND GENDER. Becker, L.A.; Parker, K.L.; Stewart, P.A.; Lawler, B.; Burns, L.N.; Yeager, J.R. Department of Psychology, University of Evansville, Evansville, IN 47722 USA. Exposure during development, to plant-derived estrogens (genistein and diadzein) can increase male rat anxiolytic behavior in the elevated plus maze (Lund & Lephart, 2001). Conversely, perinatal exposure to phytoestrogens lowers ultrasonic vocalizations (USV) emitted for neonatal rats during a 30-minute isolation from the dam and home cage (Becker, et al., 2005). This latter effect may be due to an anxiogenic effect of phytoestrogen elimination from the diet that is reversed by dietary replacement of phytoestrogens. We investigated the effects of an additional stress, environmental temperature, in a 10-minute separation paradigm to test the strength of the anxiolytic effect of phytoestrogens. Pregnant dams were fed low phytoestrogen rat chow diet (low phyto.) or the same diet and given a genistein and diadzein supplement tablet (high phyto.) from the second week of pregnancy to weaning (postnatal day 21). Offspring USV's were recorded on postnatal day 10 and again on postnatal day 15. One female and one male from each litter were tested at each temperature (22°C, 32-35°C). As well documented, there was a decrease in USV across age (Montomura et al., 2002) and with a rise in temperature (Shair, et al., 2003). Also a significant interaction between postnatal age, temperature, gender, and phytoestrogen exposure was found, suggesting that the gender-related age effect of phytoestrogens on USV is maintained with the additional temperature challenge. These data further explore the complexity of dietary phytoestrogen effects on development.

96. PARENTAL SEROTONIN 1A RECEPTOR GENOTYPE CONTRIBUTES TO ANXIETY-RELATED BEHAVIOR. Gleason G.; Bruening S.; and Toth M. Program in Neuroscience and Department of Pharmacology. Weill Graduate School of Medical Sciences. New York, NY 10065 USA. Anxiety disorders are complex neuropsychiatric diseases with both genetic and environmental components. Abnormalities in serotonin 1A receptor (5HT1A-R) signaling have been implicated in anxiety, and 5HT1A-$R^{-/-}$ (KO) mice display increased anxiety-related behavior. We utilize a novel method to disentangle genetic and environmental regulation of anxiety-related behaviors in the 5HT1A-R line, involving offspring of both non-littermate (WT parents resulting in WT offspring, KO parents resulting in KO offspring) and littermate breeding (heterozygote [HZ] parents resulting in WT and KO offspring), and factor analysis based on pup or parental genotype. WT offspring of HZ parents as compared to WT offspring of WT parents display a reduced number of open arm entries in the elevated plus maze (EPM), indicating increased anxiety, and increased stress reactivity in the forced swim test (FST). The number of center square entries in the open field exploration task, however, is regulated solely by pup genotype. We then interbred WT offspring of HZ parents, and show that their offspring also display reduced open arm behavior in the EPM and increased stress reactivity in the FST, indicating transmissibility of these behavioral phenotypes. We conclude that the 5HT1A-R may contribute to anxiety not only as a genetic but also as an environmental factor. We hypothesize that parental 5HT1A-R deficiency may affect later-life anxiety-behaviors in offspring by altering prenatal environment or modulating maternal care, perhaps through epigenetic mechanisms. We are currently conducting postnatal cross-fostering studies (WT pups to KO parents, KO pups to WT parents) to better understand the basis of parental 5HT1A-R regulation of anxiety-related behaviors.

97. PRE-ADOLESCENT SOCIAL ISOLATION INCREASES FEAR AND ANXIETY BEHAVIOR IN ADULTHOOD. Lukkes, J.L.; Mokin, M.V.; Scholl, J.L.; Forster, G.L. Basic Biomedical Sciences, Sanford School of Medicine, Univ. South Dakota, Vermillion, SD. Our previous studies demonstrated that early life social isolation (SI) enhances corticotropin-releasing factor elicited serotonergic responses from the dorsal raphe nucleus of adult rats. These findings suggest that early life stress could alter adult anxiety and stress responses. We investigated the effects of pre-adolescent SI on fear and anxiety behavior and on endocrine stress responses during adulthood. On postnatal day 21, male rats were reared either individually, or in groups of 3, for a 3-week period and then group-reared according to treatment for a further 2 weeks until early adulthood. After the 5-week treatment, adult rats were examined for anxiety-like behavior in a brightly-lit open field and in a social interaction test, or for fear behavior in a foot-shock paradigm. Isolates exhibited decreased exploratory behavior, total distance moved, and frequency to enter the center portion of the brightly-lit open field during the first ten minutes of the test period compared to group-reared rats. Isolation-reared rats also had increased latency and decreased frequency/duration in social contact, and increased freezing behavior during the 30 min social interaction test. Finally, isolates exhibited increased foot-shock-induced freezing behavior compared to group-reared rats. We also tested for immediate endocrine responses to restraint stress. Isolation-reared animals had a greater amount of pre-stress bound corticosterone (CORT), but did not differ from group-reared rats in the levels of free CORT elicited by 10 min of restraint. Overall, this study shows that isolation during the early part of development increases fear and anxiety-like behavior in adulthood and also results in alterations to basal levels of bound CORT. Support: NIH P20 RR15567& NIH RO1 DA019921.

98. INFUSION OF GROUP I METABOTROPIC GLUTAMATE RECEPTOR AGONIST WITHIN THE BASOLATERAL COMPLEX PRODUCES ANXIOLYTIC-LIKE EFFECTS IN ESTROGEN-TREATED FEMALE RATS. De Jesús-Burgos, M.I.; Ballista-Hernandez, J.; Quiñones-Laracuente, K.; Pérez-Acevedo, N.L. Anxiety is one of the most frequent forms of psychiatric disorders. The fact that females are twice affected than males suggest that gonadal hormones play a role in the etiology of anxiety-related disorders. Metabotropic glutamate receptors (mGluRs) have been involved in mechanisms associated to anxiety. mGluRs are highly expressed in the CNS, including the basolateral complex within the amygdala, a region involved in anxiety (Davidson et al., 2002). Since current treatments have many unwanted side effects, drugs acting through mGluRs may provide an alternative approach to treat anxiety. We hypothesized that group I mGluR activation within the basolateral complex modulate anxiety in a sex specific manner and that in the female rat, their effect will be modulated by estrogen. Comparison of ovariectomized female rats that receive either empty (OVX) or estradiol implants (OVX-EB); and intact male Sprague Dawley rats were analyzed in the elevated plus maze (EPM). The vehicle or (RS)-3,5-Dihydroxyphenylglycine (DHPG), a group I mGluR agonist, were bilateral infused (0.5µL/side) 5 minutes prior to the EPM. In addition, risk assessment behaviors (RABs: such as flat back approach) were recorded during the EPM. DHPG significantly increases the percent open time ($p=0.036$) and reduces the number of flat back approach ($p=0.018$) in OVX-EB. These effects were not observed in OVX or intact male rats. Taken together, these results suggest that estrogen can have a modulatory effect in anxiety related behaviors through mGluRs via basolateral complex in the fame rats. Acknowledgement: This project was partially supported by NIMH-MRISP (MH048192), RCMI (G12RR03051) and RISE

99. CHRONIC CAFFEINE AND STRESS HAVE A SEX-SPECIFIC EFFECT ON ANXIETY IN RATS. Pettenuzzo, L.F.; Noschang, C.; Crema, L.M.; Toigo, E.V.P.; Vendite, D.; Dalmaz, C. Dept. of Bioquímica, ICBS, UFRGS, RS, Brazil. Caffeine is the most widely consumed behaviorally active substance in the world and, despite its positive effects, can induce anxiety. Considering the relation between stress and anxiety and the wide utilization of caffeine by chronically stressed individuals, the objective of the present study was to evaluate the effect of chronic administration of caffeine and stress on anxiety in rats. Additionally, since behavioral and physiological responses to stress are sexually dimorphic, we conducted our studies in males and females. Wistar rats were divided into 3 groups: control (water), caffeine 0.3 g/L and caffeine 1.0 g/L (in the drinking water). These groups were subdivided into non-stressed and stressed (restraint stress during 40 days). After the treatment the rats were submitted to the plus maze and the open field tasks. Time spent in the open and closed arms of the plus maze and time spend in the central region of the open field were evaluated. Both stress and caffeine chronic treatment diminished the time spent in the open arms and increased the time spent in the closed arms of the plus maze apparatus, in male animals, without any effect in females. Caffeine also diminished time spent in the central region of the open field in males without effects in females. These observations suggest that caffeine and stress have sex-specific effects on anxiety in rats. It is not clear if the lack of effect in females is due to a protective effect, to a better coping with chronic stress and/or to a different adaptation to chronic caffeine. Thus, these results emphasize the importance of considering the impact of sex when evaluating neuropsychopharmacological parameters.

100. ACTIVATION OF VANILLOID-1 (TRPV1) RECEPTORS IN THE DORSOLATERAL PERIAQUEDUTAL GRAY ATTENUATES THE ANXIOLYTIC EFFECTS OF CANNABIDIOL. Campos, A.C.; Terzian, A.L.; Aguiar, D.C.; Moreira, F.A.; Guimarães, F.S. Dept. Pharmacology, FMRP, USP, 14049-900, Ribeirão Preto, SP, Brazil. Cannabidiol (CBD), a non-psychotomimetic constituent of Cannabis sativa, reduces anxiety when injected into the dorsolateral periaqueductal gray (dlPAG), probably by activating 5HT1A receptors. This effect, however, shows a bell-shaped dose-response curve. CBD can also activate vanilloid (TRPV1) receptors, which facilitate glutamate release. To investigate the role of these receptors in the effects induced by CBD in the dlPAG male Wistar rats received intra-dlPAG injection of capsazepine, a TRPV1 receptor antagonist (CPZ, 10-60 nmol), and were submitted to the elevated plus-maze (EPM). In a second experiment, the animals received a first injection of CPZ (10 nmol) followed by CBD (30 or 60 nmol). CPZ (60 nmol) increased the percentage of time in the open arms of the EPM, indicating an anxiolytic effect. In the second experiment, CBD (30 nmol) also produced an anxiolytic effect that disappeared when the higher dose (60 nmol) was tested. Pretreatment with an inactive dose of CPZ (10 nmol) was able to turn the ineffective dose of CBD into an anxiolytic one. These results suggest that TRPV1 receptors in the dlPAG modulate anxiety and that activation of these receptors by high doses of CBD is involved in the bell-shaped dose-response curve observed with this compound. Financial support: FAPESP, CNPq, CAPES.

101. NITRIC OXIDE SYNTHASE INHIBITOR INJECTED INTO THE DORSOLATERAL PERIAQUEDUCTAL GREY DECREASES CELLULAR AND BEHAVIORAL CONSEQUENCES OF PREDATOR EXPOSURE IN RATS. Aguiar DC, Guimaraes FS School of Medicine, University of Sao Paulo, Pharmacology, Ribeirao Preto, SP, Brazil. Nitric oxide (NO) is synthesized following activation of NO synthase (NOS) enzyme by calcium influx through glutamate NMDA receptors. NOS containing neurons are localized in the dorsolateral periaqueductal grey (dlPAG), a midbrain structure closely associated with defensive behavior. Glutamate antagonists and NOS inhibitors injected into this structure induce anxiolytic responses whereas glutamate agonists and NO donors promote flight reactions. Exposure to an innate fear stimulus (live cat) induces defensive reactions and activation of NO producing neurons in this region. The aim of this study was to test the hypothesis that the injection of the NOS inhibitor, N-ω-propyl-L-arginine (N-propyl), directly into the dlPAG would attenuate defensive reactions and local cellular activation following exposure to a live predator. Methods: Male Wistar rats (n=4-6) with cannulae aimed at the dlPAG received injections of N-propyl (100 nmol/0.2 microL) or vehicle and were exposed to a toy (control) or live cat for 10 min in a Plexiglas box. A metal grid wall located in the middle of the box prevented direct contact between the animals. An additional control group (Naïve) was left undisturbed in the home cage. After cat exposure the brains were removed and processed for cFos and NOS immunochemistry. Double-stained cells (DS) were represented as percentage of NOS positive neurons. Results: Cat exposure induced a reduction in time spent near the predator and increased immobility. It also increased cFos positive cells in both sides of dlPAG and % of DS in the contra-lateral side of injection. Pretreatment with N-propyl blocked the behavioral and cellular effects induced by predator exposure. Conclusions: These results suggest that inhibition of nitric oxide neurotransmission in the dlPAG can attenuate behavioral and cellular responses to threatening stimuli. Financial support: FAPESP, CAPES

102. ADULT HPA AXIS RESPONSIVITY TO FORCED SWIM OR ISOLATION FOLLOWING NEONATAL EXPOSURE OF RATS TO (+)-METHAMPHETAMINE C.E. Grace, M.T. Williams, C.V. Vorhees, Div. of Neurology, Dept. of Pediatrics, Cincinnati Children's Res Found and Univ Cincinnati, Cincinnati, OH, USA Methamphetamine (MA) is a psychostimulant drug that activates the hypothalamic-pituitary-adrenal (HPA) axis culminating in increased corticosterone (CORT) release. We demonstrated that rats given MA from postnatal day (P)11-15 display spatial learning and memory deficits. Others have shown that rats exposed to early stressors have altered HPA axis responses to stress and learning and memory deficits when assessed in adulthood. Therefore, we determined if MA from P11-15 also altered HPA axis development. Animals were administered 10 mg/kg MA or saline 4 times/day at 2 h intervals from P11-15. In adulthood, animals were implanted with jugular catheters 4 d prior to exposure to forced swim (FS) or isolation (ISO). FS and ISO were applied for 15 min using a counter-balanced design with the subsequent stressor applied 24 h later. Blood was taken 3 d after surgery and at 0, 15, 30, 60, 90, and 120 min after exposure to the stressors. For the FS-ISO condition, FS caused CORT to increase dramatically (peak at 30-60 min) with declining concentrations seen at 120 min. On day-2, ISO caused a smaller CORT increase (peak at 15-30 min) with return to baseline by 60 min. For the ISO-FS condition, the pattern was similar with ISO producing a smaller CORT response than FS. CORT increases on day-2 were higher relative to day-1 for each stressor suggesting sensitization. No difference was seen between MA- and saline-treated offspring. The data suggest that early MA does not lead to a permanent up- or down-regulation of later stress responsivity even though CORT is potently released during exposure (Support: DA006733 and ES07051).

103. A COMPARISON OF THE ELEVATED PLUS AND ELEVATED ZERO MAZE WITH OR WITHOUT DIAZEPAM IN RATS Amanda A. Braun, Matthew R. Skelton, Charles V. Vorhees, and Michael T. Williams, Div. Neurology, Dept. of Pediatrics, Cincinnati Children's Research Foundation & University Cincinnati College of Medicine, Cincinnati OH 45229 The elevated plus (EPM) and elevated zero mazes (EZM) are both used to assess anxiety in rodents. However, the EPM has a middle region where the animal is neither in an open or closed arm, creating an 'unscored' region, the interpretation of which is ambiguous. Shepherd et al. (1994) introduced the EZM in order to eliminate the problematic center region of the EPM. Nonetheless, a direct comparison of the two mazes has not been reported. In experiment-1, 10 untreated adult male Sprague-Dawley rats were tested in each maze. Rats tested in the EZM showed a trend toward spending more time in the open ($p = 0.07$) and exhibited more head dips than those tested in the EPM. In experiment-2, 16 animals were treated with SAL and 16 with diazepam (1 mg/kg, s.c.) 30 min before testing. Half of each group was tested in each maze for 5 min. There was a main effect of drug treatment but no effect of maze type or interaction of drug x maze. Regardless of maze, animals receiving diazepam had greater percent time in open compared to SAL. No difference was found for head dips. The results suggest that despite baseline differences in open time and head dips, both mazes are similar in sensitivity for detecting the anxiolytic effects of diazepam. The data should be interpreted with caution, however, until more animals are tested and more drugs are directly compared in these tests. (Supported by grant ES015689.)

104. THE ROLE OF ANGIOTENSINOGEN IN BEHAVIORAL DEFICITS INDUCED BY NEONATAL MDMA EXPOSURE Matthew R. Skelton, Curtis E. Grace, Tori L. Schaefer, Charles V. Vorhees, and Michael T. Williams Cincinnati Child. Res. Foundation, Cincinnati, OH. 45229 We previously showed that MDMA treatment from postnatal day (P) 11-20 leads to learning and memory deficits when the animals are tested as adults. This same treatment leads to a dysregulation in the expression of the angiotensinogen (AOGEN) gene. AOGEN has been shown to be important in learning and memory. The purpose of this experiment was to determine the effect of a knockdown of brain AOGEN on learning and memory in MDMA-treated rats. AOGEN transgenic (TG) animals that have a 90% reduction in brain AOGEN and Taconic Sprague-Dawley controls (CON) were exposed to MDMA (10 mg/kg x 4/d) or SAL from P11-20 and tested for behavioral effects beginning on P60. AOGEN TG animals, regardless of MDMA treatment, were hypoactive compared to CON. AOGEN animals spent more time in the periphery of the locomotor chamber and more time in the dark portion of the light dark chamber, suggesting AOGEN animals were more anxious than CON regardless of drug treatment. In the MWM, MDMA treatment increased latency to find the hidden platform regardless of genotype. In the CWM, MDMA treatment increased the latency of CON animals to reach the goal however there was no effect of MDMA treatment on AOGEN animals, suggesting that the knock-down of AOGEN leads to protection against MDMA's developmental effects. There was also a strain effect in that both AOGEN groups learned the CWM slower than CON animals. The results indicate that AOGEN has a selective neuroprotective effect on path integration learning (CWM) but not on spatial learning (MWM) in MDMA-treated animals. Supported by DA021394

105. COGNITION, ANXIETY, AND DEPRESSIVE-LIKE BEHAVIORS IN PET-1 KNOCK-OUT MICE. Schaefer, T.L.; Vorhees, C.V.; Williams, M.T. Div. of Neurology, Dept. of Pediatrics, Cincinnati Children's Res Found and Univ. of Cincinnati College of Medicine, Cincinnati OH 45229 Serotonin (5-HT) is involved in many developmental processes and influences behaviors including anxiety, aggression, and cognition. Disruption of the serotonergic system has been implicated in human psychological disorders including autism, depression, schizophrenia, and ADHD. Although pharmacological and dietary manipulation of tryptophan hydroxylase has greatly added to our understanding of the serotonergic system, the results are complicated by multiple factors. A newly identified ETS domain transcription factor, Pet-1, has direct control of major aspects of 5-HT neuronal development. Importantly, Pet-1 is the only known factor that is restricted to brain 5-HT neurons during development and in adulthood and exerts the dominant control over 5-HT neuronal phenotype. Disruption of Pet-1 produces an 80% loss of 5-HT neurons, a 70-80% decrease in 5-HT levels in target regions and increased aggressive behavior in Pet-1-/- mice. We hypothesized that Pet-1-/- mice would also have cognitive deficits. However, no differences in learning and memory ability in the Pet-1-/- mice tested in the Morris and Cincinnati water mazes or in novel object recognition were found. These data are surprising considering that administration of 5-HT depleting drugs such as parachlorophenylalanine, 5,7-DHT, MDMA, and fenfluramine during development all produce learning deficits. This unexpected finding may be the result of compensatory mechanisms that are invoked because the constitutive knockout is present from the inception of 5-HT neuronal differentiation. Anxiety- and depressive-like behaviors are currently being investigated. (Supported by DA021394 and ES07051).

106. MAPPING OF THE OCTOPAMINERGIC SYSTEM IN THE CNS OF THE FRESHWATER PRAWN IN THE CONTEXT OF AGONISTIC BEHAVIOR. Reyes, D.; Vázquez, N.; Rivera, N.M.; Sosa, M.A. Dept. of Anatomy & Neurobiology. University of Puerto Rico School of Medicine, San Juan, PR 00936 USA. The freshwater prawn is a crustacean that serves as a model to study the neural basis of specific behaviors. Adult males develop through 3 morphotypes (small [SC], yellow [YC] and blue claws [BC]), each representing a level in the dominance hierarchy of a group, BC being the most dominant. We are interested in understanding the role played by biogenic amines in the mechanisms underlying aggressive behavior and the establishment of dominance hierarchies. Injection of octopamine in lobsters produces postural changes related with submission. In the prawn, injection of octopamine makes a BC more submissive than a YC. Thus, octopamine may be involved in the modulation of aggressive behavior. Possible mechanisms include up- or downregulation of neurotransmitter release or of receptor expression. Here we present results on the immunohistochemical distribution of octopamine neurons in the prawn's CNS. Octopamine immunoreactivity (oct-ir) was found in the eyestalk, brain, circumesophageal (CEG), and thoracic ganglia of the SC prawn. In the CEG, two neurons with their axons were oct-ir. Four oct-ir neurons were consistently observed in T4-T5 ganglia in an area surrounding a large artery. In the medulla of the eyestalk and optic nerve, a single large-sized and a group of 10-12 small-sized neurons with their axons also showed oct-ir. Our laboratory has also cloned the first crustacean Tyr/Oct receptor, which appears to be expressed at a higher level in submissive prawns. We are now using in-situ hybridization to quantitatively map the distribution of this receptor in the prawn's CNS. MBRS S06GM008224, MRISP MH48190, RCMI G12RR03051.

107. HOUSING CONDITIONS BUT NOT PB2+ DURING THE NEONATAL PERIOD IN RATS INTERACTS WITH AN ACUTE STRESSOR ON CORTICOSTERONE RELEASE DEVON L. GRAHAM, CURTIS E. GRACE, TORI L. SCHAEFER, MATTHEW R. SKELTON, CHARLES V. VORHEES, MICHAEL T. WILLIAMS DIVISION OF NEUROLOGY, DEPARTMENT OF PEDIATRICS, CINCINNATI CHILDREN'S RESEARCH FOUNDATION AND UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE, CINCINNATI, OH Despite restrictions on the use of lead (Pb2+) in gasoline and other consumer products, Pb2+ exposure is still a problem in children, especially those of lower socio-economic status (SES). Moreover, children from lower SES families tend to be concurrently exposed to higher levels of stress, a condition that alone has been shown to be detrimental to proper development. Types of stressors may include neglect, overcrowding, or environmental impoverishment. In this experiment we tested for interactions between Pb2+ exposure and environmental impoverishment. Beginning on postnatal day (P)4, Sprague Dawley pups were raised in standard box cages containing woodchip bedding or barren cages containing only a paper towel. Pb2+ acetate (0, 1, or 10 mg/kg, freebase) was administered to the pups via gavage every other day from P4 to P11, P19, or P29. Blood Pb2+ levels were dose-dependently increased. To assess the acute stress response under the combination of Pb2+ and housing condition, animals were placed in shallow room temperature water 30 min prior to tissue collection. While Pb2+ administration had no effect on corticosterone levels, rats raised in barren cages exhibited increased basal corticosterone levels at P11 and P29 but not on P19; however there was a heightened response to the shallow water stressor at P19. The weights of the thymus and spleen, but not that of the adrenals, decreased with both Pb2+ treatment and barren conditions, indicating an effect on the immune system. Monoamine levels are currently being assessed. These data suggest that Pb2+ and stress are detrimental to development, but it is not clear whether their combined effects augment the resulting toxicity. (Supported by RO1 ES015689 and T32 ES07051)

108. INFLUENCE OF RESTRAINT STRESS ON SEROTONERGIC AND NORADRENERGIC ACTIVITY IN THE PREFRONTAL CORTEX. Cruz-Morales, S.E., García-Saldívar, N.L., González-López, M.R.A. and *Domínguez, R. Psychopharmacology, UNAM, FES-Iztacala and *UIBR, UNAM, FES-Zaragoza. The monoamines are implicated in both behavioral and physiological alterations induced by acute stress and in the process of adaptation/habituation. Exposition to stress induces changes in the concentrations of noradrenaline (NA), dopamine (DA) and serotonin (5-hydroxytryptamine, 5-HT). The prefrontal cortex (PFC) is involved in several cognitive functions. The effects of stress by restraint (R) on NA and 5-HT activities in the PFC are not well understood. The aim of present study was to analyze the effects of R on NA and 5-HT activities in the PFC of male rats. For this purpose adult male Wistar rats were randomly assigned to groups that received one of the following treatments: intact (I), 4 groups submitted to 15 or 180 min of restraint (R15; R180). The animals were sacrificed immediately 0, 1, 24 or 48 hours after the stress, the PFC dissected and NA, MHPG, 5-HT, and HIAA were measured by HPLC. NE and 5HT activities were calculated as [metabolite]/[neurotransmitter]. Compared with the intact group NA and 5-HT activities increased in the groups submitted to R (15 or 180 min) sacrificed 24h after the stress. NA activity returned to basal levels at 48 h after R (15 or 180. In R15 groups, 5-HT activity recovered after 48 h of treatment, while the increase was maintained in R180 group. Present results show that the serotonergic and noradrenergic systems in prefrontal cortex are involved in the stress response, but the response is different for each neurotransmitter. Supported by DGAPA, UNAM: IN300806.

109. GENETIC DISSECTION OF THE ROLE OF CATECHOL-O-METHYLTRANSFERASE (COMT) IN STRESS REACTIVITY IN MICE Papaleo, F.1; Crawley, J.N.2, Lipska, B.K.1; Weinberger, D.R.1; Chen, J.1 1Clinical Brain Disorders Branch; Genes, Cognition and Psychosis Program, National Institute of Mental Health, Bldg. 10, Bethesda, MD, USA. 2Laboratory of Behavioral Neuroscience, National Institute of Mental Health, Bldg. 35, Bethesda, MD, USA In humans, a single nucleotide polymorphism in the coding region of the COMT gene has been shown to produce two COMT variants: Val and Met, with higher and lower enzyme activity, respectively. Variation of COMT enzyme activity has been associated with schizophrenia, obsessive-compulsive disorder, alcoholism, bipolar disorder, suicidal behavior and pain sensitivity. We found that COMT gene deletion in mice increased reactivity to stress. In contrast, increased COMT enzyme activity in mice overexpressing the human COMT Val variant resulted in blunted stress reactivity. Genetic manipulation of COMT activity did not affect general health, locomotor activity or prepulse inhibition. We found a gene-dosage effect in stress-induced hyperthermia, in startle reaction to acoustic stimuli, in pain sensitivity and in anxiety-like responses in the elevated plus maze, with COMT-/- mice overreacting to stressful and anxiogenic-like stimuli as compared to COMT+/+ or +/- littermates. On the contrary, COMT Val overexpression reduced all these parameters of stress and emotional reactivity. Overall, the present findings reveal a critical role for COMT in stress reactivity, and may be relevant to the development of new therapeutic strategies for psychiatric illnesses.

110. BEHAVIORAL CHARACTERIZATION OF RATS BEFORE AND AFTER LEARNED HELPLESSNESS TRAINING. Eimeira Padilla, Douglas Barrett, Julio Rojas, F. Gonzalez-Lima. Institute for Neuroscience. University of Texas at Austin, Texas 78712 Inescapable shock prevents animals from learning an escape response, a phenomenon termed learned helplessness (LH). Learned helpless animals are a model of depression and post-traumatic stress disorder. Individual differences can predispose subjects to developing LH; the purpose of this study was to characterize behavioral traits that lead to LH. On day 1, rats underwent novel open field (OF) testing. On day 2, subjects were trained with inescapable shocks. On day 3, twelve rats underwent 30 trials of a fixed ratio (FR) 1 schedule, in which the escape response was a jump through a window eight centimeters from the floor. Sixteen rats underwent five FR1 trials, followed by 25 FR2 trials, in which subjects crossed twice to terminate shock. Subjects with high and low latencies to escape were classified as susceptible and resistant (respectively) to LH. On day 4, rats were re-exposed to the familiar OF. Repeated measures ANOVA on parameters related to OF behavior showed that the helpless-susceptible (S) group had greater stereotypic behavior in the periphery, especially during the familiar OF. Paired-sample t-tests revealed the (S) group reared faster after helplessness training, while (R) subjects did not. Pairwise correlations between escape latency and behavioral measures in the OF were significant for ambulatory parameters in the novel OF. S group had increased ambulatory activity, indicating that subjects who showed greater locomotor activity, were more likely to develop LH. This predisposition towards increased novelty seeking was present before the stress of learned helplessness training and testing, but not after. These results are consistent with our lab's previous findings of increased baseline locomotor activity in the congenitally helpless rat, prior to exposure to any stressors.

111. GABA-A RECEPTOR ANTAGONISM MIMICS THE EFFECT OF PROGESTERONE WITHDRAWAL ON FORCED SWIM TEST IMMOBILITY. Beckley, EH; Finn, DA. Dept. Behavioral Neuroscience. Oregon Health & Sci Univ, Portland, OR 97239 USA. Withdrawal of the steroid progesterone (PRO) increases immobility in the Forced Swim Test (FST) in female mice. Inhibiting PRO metabolism decreased concentrations of the GABAergic neurosteroid allopregnanolone (ALLO) and increased FST immobility, suggesting that PRO withdrawal may increase FST immobility through downstream ALLO withdrawal. We assessed the role of the PRO and $GABA_A$ receptors during PRO withdrawal-induced FST immobility by testing the effects of the PRO receptor antagonist mifepristone (MIF) and the $GABA_A$ receptor antagonist picrotoxin (PTX) on FST immobility among mice treated chronically with PRO. Neither 20 mg/kg MIF nor 2 mg/kg PTX increased FST immobility, alone or in combination, when coadministered with PRO (5 mg/kg) for 3 days following 5 days of PRO injections. An additional experiment determined that coadministration of PRO with 2-6 mg/kg PTX did not increase FST immobility. Following pharmacokinetic analysis of exogenously administered PRO and its metabolism to ALLO, we determined that 2 mg/kg PTX administered 60 min following PRO increased FST immobility ($F_{3,37}$=3.9, $p<.05$). These data support the hypothesis that PRO withdrawal increases FST immobility by decreasing ALLO modulation of $GABA_A$ receptors. These findings may have relevance for premenstrual syndrome and postpartum depression, which are temporally linked to rapid PRO withdrawal.

112. INDIVIDUAL VARIABILITY IN RESPONSE TO PSYCHOLOGICAL STRESSORS IN COMMON MARMOSETS. Galvão-Coelho, N. L.; Sousa M.B.C. Dept. of Physiology. Federal University of Rio Grande do Norte. Natal-RN-Brazil. It is generally expected that stressful situations cause cortisol levels to increase and later to return to basal levels. However, some studies point to individuals who present with cortisol hyperreactivity to stress situations, and low baseline cortisol levels and to other individuals who have hyporeactivity and high basal cortisol levels. These cortisol response profiles are present in healthy humans and in those who have mental disorders. In this study we investigated if common marmosets (Callithrix jacchus) with high and low (individuals who have basal means higher and lower than the group mean plus or minus one standard deviation, respectively) basal cortisol levels had this response profile. We used 32 animals (8 female dyads) and exposed them, in captivity, to three successive psychological stressors: new environment, social isolation and encounters, lasting 7 days each. The group that had high basal cortisol levels presented with cortisol hyporeactivity and reduced agonistic behaviors to a new environment. Those with low basal cortisol levels presented with hyperactivity to isolation and encounters, and increased agonistic behaviors to all stressors. Some studies consider that these exacerbated responses are not adaptive and therefore generate costs to the individuals. However, other studies consider that the hyporeactivity of cortisol is advantageous in some conditions, such as pregnant women and in individuals who are repeatedly exposed to stress situations. Further knowledge is needed to clarify this topic and to propose new protocols on how to manage these conditions.

113. ELECTROPHYSIOLOGICAL CHARACTERIZATION OF THE RAT DORSAL RAPHE-CAUDAL LATERAL WING STRESS CIRCUITRY. Vasudeva, R.K.; Waterhouse, B. D. Drexel University College of Medicine, Philadelphia, PA 19129 USA According to NIMH statistics, anxiety afflicts almost 18% of the US adult population. The neurotransmitter serotonin (5HT) is known to play a role in this disorder. The neurochemically heterogeneous dorsal raphe nucleus (DRN) is one of the main sources of 5HT to the forebrain and has been implicated in the stress response. The caudal lateral wing (cLW) sub-region of this structure is of interest because it contains a concentration of GABA- and nitric oxide synthase (NOS)-containing cells but lacks 5HT neurons. NOS cells in this area express 5HT1A receptors and are selectively activated following exposure to restraint stress, thus linking them to the stress response. The next step in understanding the role of this DRN sub-region in the stress response is electrophysiological and pharmacological characterization of cLW neurons. One hundred and seventy five neurons were recorded from the DRN, cLW and midline (ML), and ventral lateral periaqueductal grey (VLPAG) of anesthetized rats. One hundred and four of these cells met the criteria established by Allers and Sharp (2003) for GABAergic neurons. The remaining cells (n = 71) were analyzed. Neurons in cLW had spike widths that were significantly different from those recorded in ML ($p < 0.02$) and VLPAG ($p < 0.05$). Analysis of firing regularity indicated that 76% of cLW and 58% of ML neurons discharge at higher frequencies and more regularly than the remaining population. Initial experiments further show that, like 5HT neurons in other areas of DRN, cLW neurons are inhibited and excited by 5HT1A agonist and antagonists, respectively. These initial studies suggest cLW may be a functionally distinct region of the DRN that nevertheless contributes to the stress response and the operation of the DRN circuitry. As such this neurochemically distinct sub-region may prove to be an important new target for anti-anxiety medications.

114. BOTH NR2A AND NR2B SUBUNITS OF THE NMDA RECEPTOR ARE CRITICAL FOR LTP AND LTD IN THE LATERAL AMYGDALA OF HORIZONTAL SLICES OF ADULT MICE. Albrecht, D.; Müller, T. Institute of Neurophysiology, Charité - Universitätsmedizin Berlin, CCM, Tucholskystr. 2, Germany. The lateral nucleus of the amygdala (LA) as main input station to the amygdala is implicated in emotional and social behaviors, especially those related to fear. We have recently shown in rodent horizontal brain slices that activation of NMDA receptors (NMDARs) is a requirement for persistent synaptic alterations in the LA, such as long-term potentiation (LTP) and long-term depression (LTD). In the LA NR2A- and NR2B-type NMDRs coexist in synapses of LA projection neurons. Using a pharmacological approach we assessed the contribution of the two NMDAR subtypes to LA-LTP and LA-LTD in adult mouse horizontal brain slices by different induction protocols, by different inputs to LA neurons and in the presence of NMDAR subunit antagonists (NVP-AAM 077, Co 101244, Ro 04-5595). We show for the first time that paired pulse (interstimulus interval: 40 ms) low frequency stimulation of external capsule fibers causes stable LA-LTD. In general, our results indicate that both NR2A and NR2B subunits are required for the formation of LA-LTP and LA-LTD and the abolishment or reduction of plasticity changes by these compounds could be due to the reduction in calcium influx via NMDARs. Thus, rather than resulting from exclusive roles of NMDAR subtypes, the synaptic plasticity response in the amygdala appears to be directed by the pattern of synaptic activation and the used input, which recruit the major NMDAR subtypes to variable extents and triggers distinct signalling cascades.

Saturday, June 21, 2008

8:30-10:30 Symposium 5: Sensory and peptidergic control of food hedonics: Relation to eating disorders. Chair: Sarah F. Leibowitz.

RELAPSE TO FOOD SEEKING: ROLE OF CRF, PYY3-36 AND HYPOCRETIN (OREXIN) Sunila Nair, Udi Ghitza and Yavin Shaham Behavioral Neuroscience Branch, NIDA/IRP/NIH/DHHS, Baltimore The major problem in treating obesity is high rates of relapse to maladaptive eating habits during dieting; this relapse is often induced by stress states or acute exposure to palatable food or food cues. Preclinical studies have not explored this clinical problem. We recently adapted the reinstatement procedure (commonly used to study relapse to abused drugs) to examine mechanisms underlying stress-induced relapse to food seeking. In our studies, rats on a restricted diet (~65-75% of daily intake) are trained for 9-12 days (6-9 h/d, every other day) to lever-press for 45 mg fat pellets (25-35% fat) under a fixed-ratio 1 (20s timeout) schedule. They are then given 10-20 daily non reinforced extinction sessions. During subsequent reinstatement tests, the rats are injected with yohimbine (2 mg/kg), an alpha 2 adrenoceptor antagonist that induces stress and anxiety in humans and nonhumans, or given 1-5 food pellets non-contingently (a food taste cue). Yohimbine injections and pellet priming reliably reinstate food seeking. In initial studies, we assessed the role of corticotropin-releasing factor 1 (CRF1) receptors, peptide YY(3-36), and hypocretin 1 receptors in yohimbine- and food priming-induced reinstatement. Our results indicate a role of CRF1 receptors in yohimbine- but not food priming-induced reinstatement, and of peptide YY(3-36) in food priming- but not yohimbine-induced reinstatement. To this end, we found no evidence for a role of hypocretin 1 receptors in yohimbine- or food priming-induced reinstatement. Overall, our data suggest a potential dissociation between the neuronal mechanisms that mediate stress-induced relapse versus food-priming-induced relapse to high-fat food seeking.

PEPTIDERGIC CONTROL OF FORAGING AND HOARDING. Bartness, T. J.; Dailey, M.J.; Keen-Rhinehart, E. Dept. of Biology, Georgia State University, Atlanta, GA 30302-4-10 USA. Food almost always has to be acquired (foraged) and frequently is stored (hoarded); however, the mechanisms underlying these appetitive behaviors are virtually unknown relative to those underlying food intake (consummatory behavior). Using a simulated burrow system with a wheel running-based foraging requirement, we are identifying the peptidergic control of these behaviors in Siberian hamsters. This species does not increase food intake after food deprivation, but instead increases foraging and hoarding providing a naturally-occurring separation of appetitive from consummatory ingestive behaviors. The food deprivation-induced increases in foraging/hoarding are duplicated in fed hamsters given the stomach-derived peptide, ghrelin peripherally, and when neuropeptide Y (NPY) or agouti-related protein (AgRP) are injected into the 3rd ventricle. 3rd ventricular subthreshold doses of NPY and AgRP that do not affect these behaviors singly significantly increase foraging and hoarding when given together suggesting an underlying common neural substrate. NPY microinjections into the hypothalamic paraventricular nucleus (PVH) decrease foraging, but increase hoarding and food intake, whereas microinjections into the perifornical area (PFA) increase all three behaviors with food hoarding stimulated to the greatest extent. PVH and PFA Y1 receptor antagonism inhibit post food deprivation-induced increased food hoarding and in the PFA inhibit foraging as well. Destruction of all NPY Y receptor-containing neurons within the PVH using NPY conjugated to saporin (NPY-SAP) decreases foraging and food hoarding under baseline conditions with no change in food intake. PVH NPY-SAP inhibits post-food deprivation induced increases in foraging and hoarding. Destruction of the arcuate nucleus (Arc) either by NPY-SAP or neonatal administered monosodium glutamate both result in significantly exaggerated food deprivation-induced increases in hoarding especially early in the refeeding period, likely due to an increase in PVH/PFA Y1 receptor number/affinity. Collectively, these results begin to identify some of the peptides and their sites of action underlying foraging and hoarding.

OVERCONSUMPTION OF FAT: CIRCULATING LIPIDS AND BRAIN NEUROCHEMICALS IN A VICIOUS CYCLE. Leibowitz, S.F. The Rockefeller University, New York, NY 10021 USA Recent studies in our laboratory have identified possible mechanisms underlying the overconsumption of a fat-rich diet. When injected into the hypothalamic paraventricular nucleus (PVN) of rodents, the peptides galanin, orexins and opioids (enkephalin and dynorphin), which are known to stimulate eating behavior, are found to produce a significantly stronger effect on a high-fat compared to low-fat diet, with the receptor antagonists producing the opposite effect. Furthermore, chronic consumption of a fat-rich diet, a single fat-rich meal, or injection of a lipid emulsion, in turn, stimulates these endogenous peptides specifically in the PVN, and this effect is closely, positively associated with the rise in circulating triglyceride levels. When repeated over several days, consumption of a single high-fat meal compared to an equicaloric low-fat meal, while elevating circulating lipids, significantly increases 24-hour food intake, even on a chow diet. These findings support the existence of non-homeostatic, positive feedback circuits, or "vicious cycles", that relate dietary fat and circulating lipids to hypothalamic peptides that potentiate feeding. Together with recent evidence showing these peptides to stimulate the release of forebrain dopamine, these results suggest that these hypothalamic systems contribute to the overeating associated with fat-rich foods. Normal-weight rats with consistently higher triglycerides after a fat-rich meal show increased expression of these peptides and increased propensity to overeat and gain weight on a chronic high-fat diet. The additional findings, that these peptides are already elevated in pre-pubertal rats with increased risk for overeating as adults and are reduced by intake of triglyceride-lowering, polyunsaturated fat diets, suggest possible means for controlling consummatory behavior and combating the epidemic of childhood obesity.

NEUROTRANSMITTER SYSTEMS IN THE SEEKING AND CRAVING FOR SUGAR AND ALCOHOL. Hoebel, B.G.; Avena, N.M.; Rada, P.V. Dept. of Psychology, Princeton University, Princeton, NJ 08540, USA. Food addiction is plausible because brain pathways that evolved to respond to natural rewards, such as food, are also activated by addictive drugs. Sugar and alcohol are noteworthy as caloric substances that release opioids and dopamine and thus have addictive potential. Bingeing, withdrawal and craving are three phases of addiction that can be operationally defined and measured in rats using sugar as the reinforcer. Bingeing with 10% sucrose releases dopamine repeatedly and leads to neurochemical changes in the brain that also occur with addictive drugs. These include alterations in dopamine and opioid receptor binding, enkephalin mRNA expression and dopamine and acetylcholine release in the nucleus accumbens. During withdrawal, anxiety and behavioral depression are observed. During prolonged sugar abstinence, as with alcohol abstinence, reinstatement causes greater intake than ever before. This causes a binge eating cycle that may translate to human conditions, as suggested by the similarity to some eating disorders. Supported by PHS grants MH-65024 and AA-12882.

11:00-12:00 Keynote Lecture: Ian Q. Whishaw

SKILLED FORELIMB USE IN THE RAT AS USED TO MODEL HUMAN NEUROLOGICAL CONDITIONS. Ian Q. Whishaw, Canadian Centre for Behavioural Neuroscience, University of Lethbridge, Alberta Canada Skilled forelimb movements are evolutionarily conserved likely dating to the first terrestrial vertebrates. The movements of the arm, hand, and digits, as they are used to reach for food for eating, are similar in the sister clades of rodents and primates. Thus, rat skilled reaching can be used to model a number of human neurological conditions. Rat skilled reaching movements have been described using a variety of movement notation systems, using high speed video recording methods, and using cineradiography. Skilled reaching behavior is complex and consists of a number of oppositions (stimulus response relationships), between the rat and the food target, a number of forelimb gestures (non-weight supporting movements), which are performed to obtain food, and a complex series of segmental movements (of the limb, head, and trunk), all of which influence the success of the act. Measures of these four aspects of skilled reaching behavior following motor system injury reveal that there are a number of learned changes that take place at different times, including learned nonuse, learned bad-use, and forgetting. These aspects of behavior can be related to compensatory and plastic changes that take place following injury. Additionally, theses aspects of behavior can be used to investigate rehabilitative and therapeutic treatments for brain injury.

2:30-4:30 Symposium 6: Transational research on sexual functions: Is it possible? Chairs: Anders Agmo and Raul Paredes.

SEX IN MICE AND MEN: BASIC MECHANISMS AND BEHAVIORAL EXPRESSIONS. Anders Ågmo, Dept. of Psychology, University of Tromsø, Norway. Sexual behavior consists of two qualitatively different processes. One, approach to a potential mate and the establishment of initial contact, involves contextually determined, essentially arbitrary motor patterns. A woman or a female rat may approach a male in any number of different ways, for example. The second process, copulation, involves a series of highly stereotyped, frequently species specific, motor patterns in most mammals. It is believed that primate copulatory behavior is less stereotyped than that of other mammals. Among the primates, the human shows an unusually large variation in copulatory motor patterns. In fact, only the creativity of the human mind and the athletic capacities of the individual impose limits on these patterns. Despite the chasm between human and non-human copulatory behavior, there are several reasons for believing that the basic mechanisms controlling its occurrence and intensity are similar among all mammals, at least. As far as we know, the brain structures and the neurotransmitters involved as well as the basic behavioral mechanisms of motivation, reinforcement and reward are similar. Other mechanisms involved in sexual behavior, like erection and vaginal lubrication, seem also to be most similar among mammals. This similarity suggests that results from neurobiological and pharmacological studies of non-human, mammalian sexual behaviors can be applied to the human. Data from behavioral studies are probably as relevant as other kinds of data. Studies in the human suggest that some sexual dysfunctions or unusual sexual behaviors are consequences of behavioral events. A history of absent sexual reward may lead to hypoactive sexual desire disorder, while fetishism is easily explained as a result of classical conditioning, just to mention two examples.

NITRIC OXIDE IN ERECTILE DYSFUNCTION: TRANSLATING PATHOGENETIC CONCEPT INTO THERAPEUTIC APPROACH. Dugina, J.L.; Zhavbert, E.S.; Kheyfets, I.A.; Sergeeva, S.A.; Epstein, O.I. Materia Medica Holding Company. 9, 3-rd Samotyochnyi per., Moscow, 127473 Russia. Diabetes, aging, hypercholesterolemia, hypertension, erectile dysfunction and some other pathological conditions are associated with the impairment of vascular function. Nitric Oxide (NO) is an important factor in regulating vascular tone. In the endothelium the main source of NO is endothelial NO synthase (eNOS). Mechanisms that possibly related to a loss in endothelial NO bioavailability include decreased eNOS expression and/or activity, dysregulation of eNOS phosphorylation, eNOS uncoupling, decreased levels of eNOS cofactors and substrate, impaired interaction of eNOS with its endogenous regulators. eNOS activation by calcium/calmodulin accounts for rapid and transient production of endothelial NO; phosphorylation of Ser1177 of eNOS (Ser1179 of bovine eNOS) can be attributed to eNOS activation in the absence of a sustained increase in intracellular calcium. There are several possible approaches to restore eNOS functionality/expression. These include regulation of eNOS phosphorylation; use of supplementation with eNOS cofactor BH4, folic acid or vitamin C that are able to recouple eNOS; controlling of endogenous regulators network etc. The impact of pharmacogenomics is also should be taken into consideration. A novel method for treating ED by regulation of eNOS activity is developed. Ultra-low doses of antibodies to eNOS (to C-terminal region comprising 1185-1205 aa of bovine eNOS) were used to enhance eNOS activity. Preclinical studies showed their influence on NO-cGMP pathway and their ability to enhance erectile function and sexual motivation in animal models. In clinical trials the correlation of ED severity and treatment efficacy with asymmetric dimethylarginine (ADMA) concentration in serum and eNOS gene polymorphism was studied.

CHALLENGES OF DEVELOPING PRECLINICAL RODENT MODELS OF SEXUAL MOTIVATION FOR DRUG DISCOVERY PURPOSES Darlene C. Deecher Wyeth Research, Collegeville, PA 19426. Female Sexual Dysfunction (FSD) is a multifactorial condition with anatomical, physiological, psychological and social components. There are 4 subcategories of FSD: sexual desire, arousal, orgasm, and dyspareunia. Hypoactive sexual desire disorder (HSDD), commonly referred to as low libido, is the most prevalent form of FSD across all age groups (Laumann et al. 1999). The DSM-IV definition of HSDD is described as a persistent or recurrent absence of sexual fantasies and desire for sexual activity that results in marked distress or interpersonal difficulty (Hayes RD et al. 2006). Currently, no HSDD products are registered within the US. Thus, there is a need to develop therapies that can alleviate HSDD. Animal models are necessary in order to provide some degree of confidence and guidance for target identification and screening in drug discovery. In order to develop animal models suitable to evaluate putative targets involved in sexual motivation and for the purpose of compound screening with acceptable throughput, there are several key factors to consider. The measurements selected must be robust and reproducible. Additionally, they must be amendable to compound screening that can support a drug discovery program, with all aspects of resources such as time investment, number of animals required per data point and manpower considered. This talk outlines these considerations for developing preclinical models of sexual motivation for drug discovery purposes and will describe a specific example of model development using a partner-preference measurement. From our experience, it is clear that current models are cumbersome and not ideal for drug screening. Future efforts to develop these models should consider the feasibility of each measure and the simplicity of experimental design. Future success in developing agents that will treat women experiencing HSDD, will require preclinical models that are predictive of clinically meaningful endpoints (e.g. sexual satisfaction and improved desire).

CONTROL AND SEXUAL REWARD IN RATS, CAN THAT BE TRANSLATED TO HUMANS? Raúl G. Paredes. Instituto de Neurobiología, UNAM Campus Juriquilla. Querétaro Qro. México. The ability to control the rate of sexual stimulation in male and female rats is crucial for the development of a reward state associated with mating. We have consistently used the conditioned place preference paradigm (CPP) to evaluate the positive affect induced by mating under different conditions. In our testing conditions sexual behavior occurs in a mating cage and the animals are gently transferred to the conditioning cage. In this way we is evaluate the physiological state induced by mating. Only when subjects are able to pace the sexual interaction CPP is produced. In the case of the female, ten paced intromissions are sufficient to induce a reward state and progesterone is crucial for sex to be rewarding. The opioid antagonist naloxone blocks the CPP induced by mating in both male and female rats, suggesting that the reward state induced by mating is mediated by opioids. Mating in the rat has evolved in such a way not only to assure physiological changes that will favor gestation, but also to enhance the rewarding aspects of mating that make sex a natural reinforcer. Studies in humans indicate that women that report being controlled in a relationship find sex less satisfactory.

6:00-7:00 IBNS Fellows Symposium

A BEHAVIORAL HOMEOSTASIS THEORY OF HABITUATION AND SENSITIZATION: CAN IT BE USEFUL IN THE EARLY DIAGNOSIS OF ALZHEIMER'S AND OTHER COGNITIVE DISORDERS? Eisenstein, E. M.; Eisenstein, D. L.; Sarma, J. S. M. VA Greater Los Angeles Healthcare System, CA 90073, USA. The 'behavioral homeostasis theory' (BHT) can explain why the learned behaviors of habituation and sensitization occur throughout phylogeny to iterative stimuli. One of its postulates is that pre-initial stimulus 'alertness' influences both the magnitude of response to the first stimulus of a new repetetive series as well as the direction of behavioral change to the following stimulus, i.e. a continuum ranging from 'habituation' through 'no directional change' to 'sensitization'. Thus, high initial responders tend to habituate to an insignificant stimulus and low initial responders tend to sensitize. The level of responsiveness achieved in both initial habituaters and sensitizers as an asymptote is approached is a 'behavioral homeostatic balance' between being too sensitive and attentive to an unimportant stimulus and missing other significant stimuli, and being too insensitive and missing a change in the relevance of the present stimulus. A lack of response change over initial trials (null point) is postulated to be the result of an 'optimal alertness level' for receiving and initially assessing a new stimulus in normal individuals. This occurs when the individual is able to receive and initially assess a new stimulus without the need for any 'behavioral homeostatic change' (habituation or sensitization). Aberrations in these learned behavioral changes to repetetive stimuli may be clinically useful. Thus, using an inexpensive and simple autonomic response measure such as the galvanic skin response (GSR) to an iterative stimulus such as a tone, could be helpful in the early diagnosis and assessment of treatment effectiveness in memory disorders such as Alzheimer's as well as in other cognitive abnormalities. This also would eliminate the need for verbal communication between the patient and caregiver.

PLASTIC EFFECT OF LEPTIN ON THE HIGHER BRAIN FUNCTION. Oomura, Y.; Aou, S.; Fukunaga, K. Dept. Integrative Physiology, Faculty of Med, Kyushu Univ. Fukuoka, Life Sci., Kyushu Institute of Tech., and Dept. Pharmacol. Faculty of Pharmaceu., Tohoku Univ. Sendai The concentration of leptin increases from 10^{-10} to 2.4 x 10^{-10} M during food intake. Only one thousandth of leptin enters into the brain. The increased leptin, about 10^{-12} M first arrives to the satiety and feeding centers and facilitates neurons in the former and inhibits those in the latter center. Thus leptin is one of endogenous satiety substance. Then leptin reaches to the hippocampus and learning and memory function, namely the passive avoidance and water maze tasks are facilitated. At that time long-term potentiation in the CA1 neurons and phosphorylation of calmodulin kinase II in the hippocampus are both facilitated. The pharmacological dose of leptin, 10^{-10} M, inhibits these effects oppositely. In addition Zucker rats and db/db mice who have the abnormal leptin receptors can not produce learning and memory tasks and long-term potentiation. Therefore food intake necessary for not only to keep the body homeostasis but also for the facilitation of the plasticity in the higher brain function.

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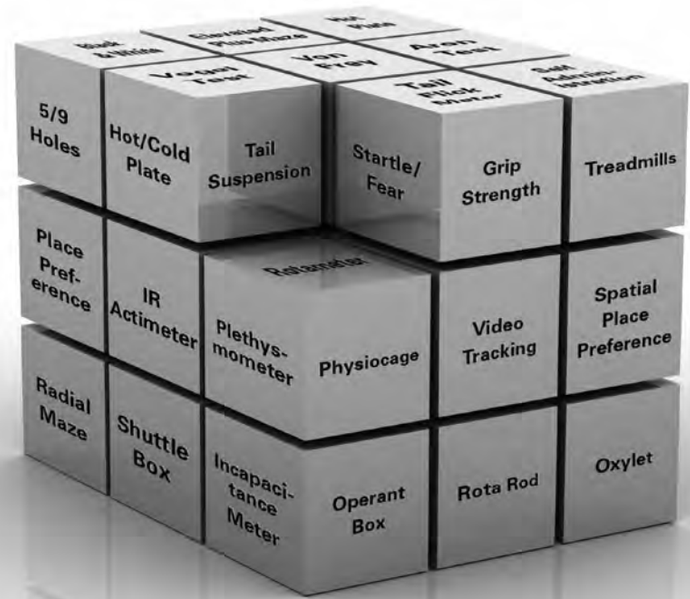

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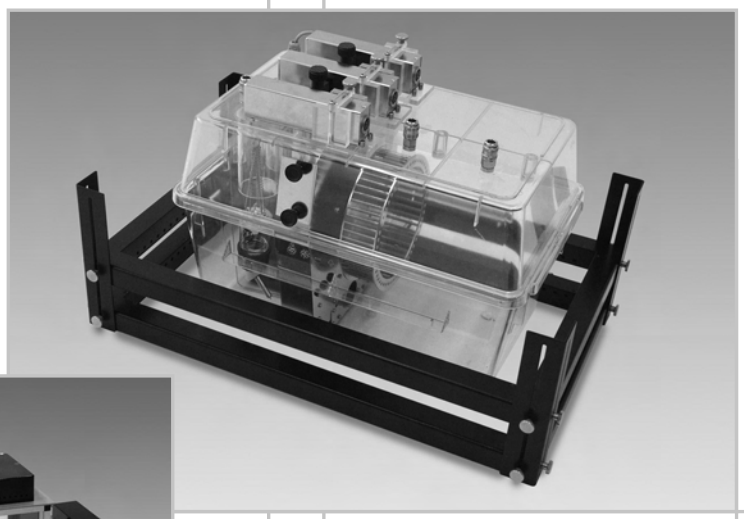

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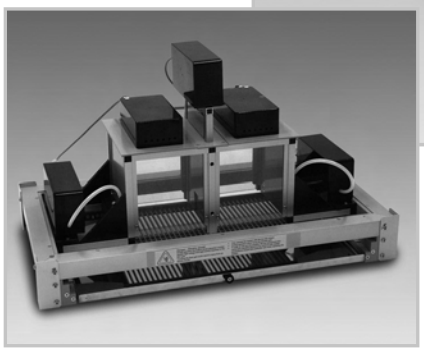

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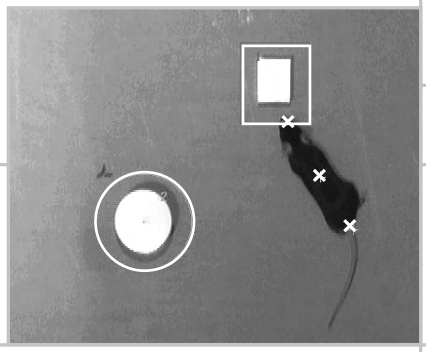
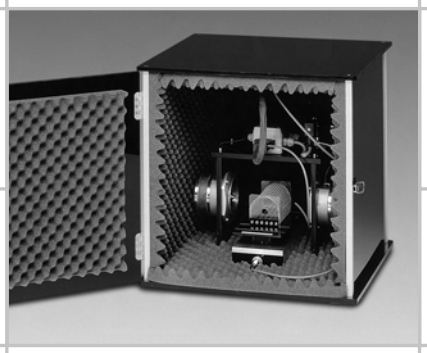


■ *VideoMot2 - 3-Point-Tracking*



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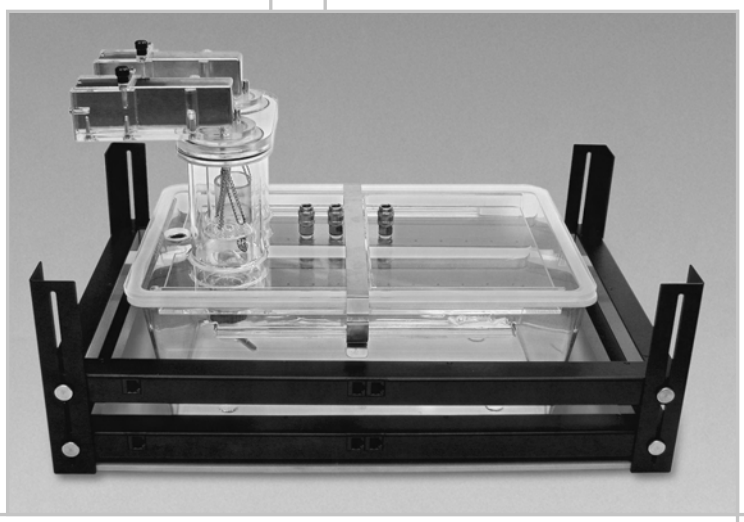
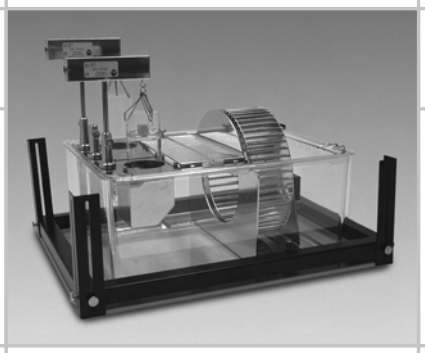
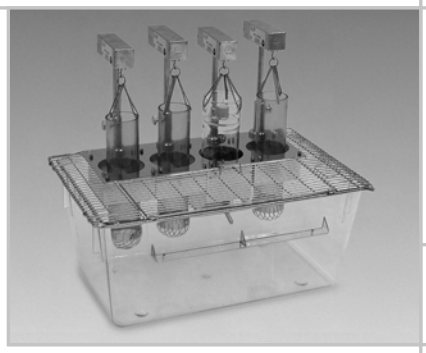


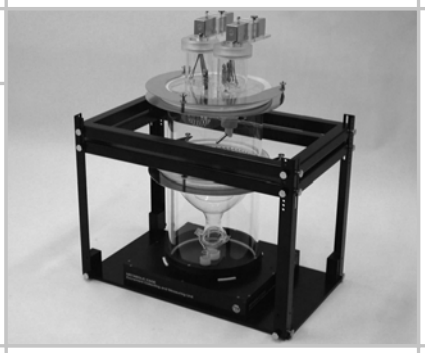
■ *CaloCage with Drinking & Feeding Sensors and Activity Frame*



■ *Combined Home Cage & Wheel Activity*



■ *Choice Preference Configuration*



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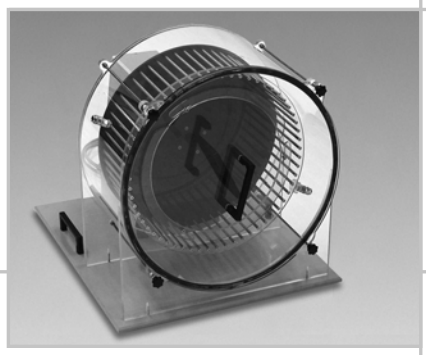

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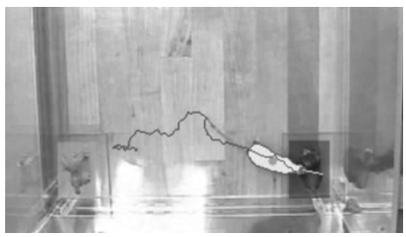

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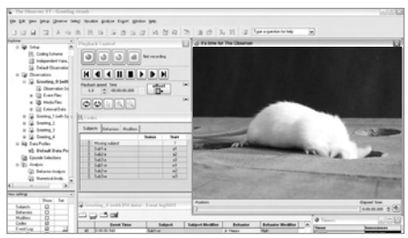

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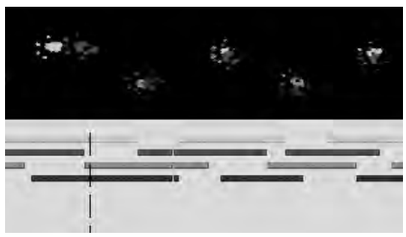

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1. HM Kamens et al (2005) Characterization of the parallel rod floor apparatus to test motor incoordination in mice. *Genes, Brain and Behavior* **4**, 253–266

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IBNS Program (short version)

All events will be held in the Harbour Ballroom unless otherwise noted.

Tuesday, June 17, 2008

8:00-12:00 **Council Meeting** - Cellar Room
1:00-3:00 **Registration** - Harbour Concourse
4:00-6:00 **Student Social** – Sea Side Suite
7:00-9:00 **Registration** - Harbour Concourse

Wednesday, June 18, 2008

8:30-9:00 **President's Welcome**, Robert Gerlai
9:00-10:00 **Keynote Lecture**, David Amaral
10:00-10:30 **Break & Exhibit Viewing**
10:30-12:30 **Symposium 1**: Stress and anti-stress systems in the regulation of alcohol seeking
12:30-2:00 **Break**
2:00-2:30 **Grant Workshop**
2:30-4:30 **Student Workshop**
4:30-5:00 **Break & Exhibit Viewing**
5:00-6:30 **Oral Session 1:** Motivation: Addiction and anxiety
6:30-8:00 **Cocktail Reception** - Sea Cliff Terrace

Thursday, June 19, 2008

8:30-10:30 **Symposium 2**: Neuroactive steroids in mental illnesses and drug abuse
10:30-11:00 **Break & Exhibit Viewing**
11:00-12:00 **Matthew J Wayner-NNOXe Pharmaceuticals Award Lecture,** Stephen B. Dunnett
12:00-4:00 **Break**
4:00-6:00 **Student Travel Award Slide Blitz**
6:00-8:30 **Poster Session 1**

Friday, June 20, 2008

8:30-10:30 **Symposium 3**: Glial-neuron interactions in neuropsychiatric and neurodegenerative diseases
10:30-11:00 **Break & Exhibit Viewing**
11:00-12:15 **Oral Session 2:** Learning, memory and motor systems
12:15-4:00 **Break**
4:00-6:00 **Symposium 4**: Animal modeling of cognition: Relevance to schizophrenia
6:00-8:30 **Poster Session 2**

Saturday, June 21, 2008

8:30-10:30 **Symposium 5:** Sensory and peptidergic control of food hedonics: Relation to eating disorders
10:30-11:00 **Break & Exhibit Viewing**
11:00-12:00 **Keynote Lecture**, Ian Q. Whishaw
12:00-2:30 **Break**
2:30-4:30 **Symposium 6:** Transational research on sexual functions: Is it possible?
4:30-5:00 **Break**
5:00-6:00 **IBNS Business Meeting**
6:00-7:00 **IBNS Fellows Symposium**
7:00-11:00 **IBNS Banquet**

Future IBNS Meetings:

June 9-14, 2009
Wyndham Grand Bay - Isla Navidad Resort
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2010 is still in negotiations
but will be in Europe.