International Behavioral Neuroscience Society

Program/Abstracts

June 16-20, 2004
Key West, Florida, USA

Abstracts of the International Behavioral Neuroscience Society, Volume 13, June 2004

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..... Robert Gerlai
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CONTENTS

Dear Colleagues,

Welcome to the 13th annual meeting of the International Behavioral Neuroscience Society. I am certain that each of you will be able to find an exciting variety of papers, talks, symposia, and satellites at this meeting. The presentations here represent almost every field in our area, and attendees will constitute an array of disciplines and approaches, in addition to countries of origin. The people and the research presented at this meeting will provide an outstanding opportunity for cross-disciplinary interaction, for learning and for dissemination of findings.

This outcome owes a great deal to the meeting organizers. I would like to extend personal thanks to Gary Coover, Program Chair, and to Marianne Van Wagner, our institutional memory and executive, for efforts far beyond the call of duty. There are many others, whom I will not list but hope to thank personally, for their efforts to make this the best meeting yet.

Key West is an exciting venue, new to me and many others but promising both history and contemporary excitement, not to mention blue crabs. We are anticipating high levels of attendance, spilling out from our meeting hotel to others in the area, and a good –and scientifically profitable—time is expected by all. I am happy to welcome each of you here.

Bob Blanchard
President IBNS

We are pleased to announce the recipients of the IBNS Travel Awards for the 2004 meeting in Key West, Florida. These awards will be presented at the Conference 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 by category and alphabetically)

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

Postdoctoral

Sheila Fleming, *The David Geffen School of Medicine (UCLA), USA*
Miriam Hickey, *The David Geffen School of Medicine (UCLA), USA*

Graduate

Ashley Acheson, *University at Buffalo, USA*
Nicole Avena, *Princeton University, USA*
Paul Lee, *University of Maryland, Baltimore, USA*
Lauren Levy, *Yale University, USA*
Catherine Lowry, *University of Chicago, USA*
Chris Markham, *University of Hawaii at Manoa, USA*
Tammy Moscrip, *Columbia University, USA*
Victoria Risbrough, *University of California, San Diego, USA*
Mu Yang, *University of Hawaii at Manoa, USA*

Undergraduate

Catherine McNutt, *Northern Kentucky University, USA*
Tori Schaefer, *Cincinnati Children's Hospital Research Foundation, USA*

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

The IBNS would like to express our gratitude to the following organization who has given financial support to the 13th International Behavioral Neuroscience Society Conference. This financial support enabled many students to attend the conference and also allowed recruitment of excellent special symposium speakers.

National Institute of Mental Health

The IBNS would like to express our gratitude to the following exhibitors, publishers and corporate sponsors (in bold/italics) that are attending or have books and materials on display, and/or have given special support to the 13th International Behavioral Neuroscience Society Conference:

Clever Sys. Inc.

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Research Diets, Inc.

SciPro Inc.

Viewpoint Life Sciences Inc.

The IBNS was formed to encourage research and education in the field of behavioral neuroscience. In support of this goal, the following members contributed towards the student travel awards for the Key West meeting.

MEMBER CONTRIBUTIONS OVER $100

Mark A. Geyer
Robert D. Myers
Michael L. Woodruff

MEMBER CONTRIBUTIONS

Sally Anderson
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ACKNOWLEDGMENTS

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

PROGRAM COMMITTEE:

Gary Coover (Chairperson); Markus Heilig (Co-Chair); Tim Moran; Alain Gratton; Athina Markou; Sue Carter; Marcus Brandao; Klaus-Peter Ossenkopp; Emmanuel Onaivi; Jacques Abraini; Paul Rushing; Jacqueline Crawley; Caroline Blanchard; Anna Lee (Student).

LOCAL ORGANIZING COMMITTEE:

Doug Shytle (Chairperson); Ronald F. Mervis; Cesar V. Borlongan; Allison Willing; Michael E. Smith; Mary Newman; Angel Jenkins.

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Robert Gerlai (Chairperson); Robert Adamec (Co-Chair); Kyle Frantz; Francisco Gonzalez-Lima; Vickie Risbrough (Student); Susan Powell; Martin Sarter; Pascual Gargiulo.

SCIENTIFIC PROGRAM

KEYNOTE SPEAKERS

- **Michael Davis** - Emory University
  Neural systems involved in fear, anxiety and extinction

- **George Koob** - The Scripps Research Institute
  The dark side of addiction: Neuropharmacological disruption of the brain reward and stress systems

- **Paul Sanberg** - University of South Florida
  Novel cell therapy approaches for brain repair

PRESIDENTIAL ADDRESS

Robert Blanchard, The University of Hawaii. *The organization and modeling of defensive behavior*

SPECIAL SYMPOSIA

- **Factors influencing the acceleration and delay of aging.** *Co-Chairs*: Susan A. Farr and William Banks, St. Louis University School of Medicine, St. Louis, MO, USA.

- **Modeling abnormal brain and behavior development: When more is better.** *Co-Chairs*: Mikhail V. Pletnikov, Johns Hopkins University School of Medicine, and Christine F. Hohmann, Morgan State University, Baltimore, MD, USA.

- **Estrogen: Old hormone, new tricks.** *Chair*: C. Sue Carter, University of Illinois at Chicago, Chicago, IL, USA.

- **From complex phenotypes to genes: Finding the links in dependence and emotionality.** *Co-Chairs*: Markus Heilig, NIAAA, Bethesda, MD, USA/Karolinska Institute, Stockholm, Sweden; & Rainer Spanagel, Institute of Mental Health, University of Heidelberg, Mannheim, Germany.

- **Introduction to behavioral measures of impulsivity for neuroscience.** *Chair*: Donald M. Dougherty

SATELLITES

June 15-16. Defensive Behavior. (Coral Reef Room) Organizers: **Robert Adamec**, Memorial University, Canada; **Robert J. Blanchard**, University of Hawaii, USA; **Newton S. Canteras**, University of Sao Paulo, Brazil; & **Iain S. McGregor**, University of Sydney, Australia.

Introduction:
Robert J. Blanchard – University of Hawaii

Perspectives on Defense:
Frederico G. Graeff – University of Sao Paulo. Defense and anxiety disorders.

Predatory Odor Effects on Defense: Reactions to Predatory Odor:
Raimund Apfelbach – University of Tubingen. Predator odor and its impact on fertility and reproduction in the Phodopus hamster.

Markus Fendt - University of Tubingen. Fear behavior induced by fox odor: Behavioral and neurobiological characterization.

Iain S McGregor – University of Sydney. The neural basis of cat odor induced defensive behaviors in rats: Conditioned versus unconditioned effects.

Neural Systems Modulating Defensive Behavior:
Robert Adamec – Memorial University. Contributions of NMDA receptors and individual differences in vulnerability to lasting brain and behavioral response to predator stress.

D. Caroline Blanchard – University of Hawaii. Neural Systems: Antipredator Defense.
Marcus Lira Brandao – University of Sao Paulo. GABAergic regulation in the neural organization of fear in the midbrain tectum.

Newton S Canteras – University of Sao Paulo. The 'cat exposure paradigm': Neural system analysis.

Francisco Silveira Guimaraes – University of Sao Paulo. Role of nitric oxide on defensive reactions.

Luiz Carlos Schenberg – University of Sao Paulo. Organization of single defensive behaviors within distinct structures of brain defense systems: Role of NMDA glutamate receptors.

Lorey K Takahashi – University of Hawaii. Amygdala modulation of unconditioned and conditioned fear.

Genetic Control of Defensive Behavior:
Andrew Holmes – National Institute of Health. Genetic variation in serotonin transporter function and risk for emotional disorders: Evidence from gene mutant mice.

Andre Ramos – University of Santa Catarina. Emotional reactivity in rats: the search for genes.

Psychopharmacology and Defense:
Catherine Belzung – University of Francois Rabelais. Guy Griebel - Sanofi Synthelabo. Vasopressin V1b receptor blockade and anxiety related behaviors.

Antonio de Padua Carobrez - Univ. of Santa Catarina. Is the periaqueductal gray matter key to expression of one trial tolerance to anxiolytics?

Comparative Studies of Defense:
David Eilam – University of Tel-Aviv. Antipredator defenses to avian predators.
Martin Kavaliers – University of Western Ontario.

Defensive Ultrasound:
Stephan Brudzynski – Brock University. Acoustic characteristics of the air puff-induced 22 kHz alarm calls in direct recordings.

Kindling and Defense:
Lisa E Kalynchuk - Dalhousie University. Computational modeling of defensive behavior on an elevated plus maze.

Learning and Defensive Behavior:
Michael S Fanselow – UC Los Angeles. Stress-induced enhancements of learned defensive behaviors.

June 16. Nicotine as a Therapeutic. Agent in Mental and Neurological Disorders. (Big Pine-Conch Room) Organizers: **Russell W. Brown** and **Michael L. Woodruff**. East Tennessee State University.

Maryka Quik, The Parkinson's Institute: "Nicotinic receptors, the nigrostriatal system, and Parkinson's disease."

Paul Newhouse, University of Vermont School of Medicine. "The efficacy of novel nicotinic agonists in treatment of behavioral disturbances in the elderly."

Jim Pauly, University of Kentucky College of Pharmacy. "Nicotine and its effects on recovery of function after brain injury."

Edward Levin, Duke University Medical Center. "Nicotinic treatment for cognitive dysfunction."

Edna F.R. Pereira, Luis E.F. Almeida, Maristela de Oliveira, Edson X. Albuquerque, University of Maryland Sch Med. "Functional and structural charges induced by nicotine in the hippocampus."

Nii Addy, graduate student, Yale University Dept. of Psychiatry. "Is Calcineurin involves in nicotine-induced plasticity?"

Reba Rubenstein, graduate student, Yale University Dept. of Psychiatry. Title to be announced.

Douglas Shytle, University of South Florida College of Medicine. "Neuronal Nicotinic Receptors as Targets for Antidepressants"

Scott Rogers, University of Utah School of Medicine. Title to be announced.

Russell Brown, East Tennessee State University Dept. of Psychology. "Nicotine eliminates cognitive deficits in rodent model of schizophrenia and brain injury."

Dr. Sharon Grady, University of Colorado "Diversity of nicotinic acetylcholine receptors: potential for selective therapy"

WORKSHOPS

NIH Grant Workshop: Israel Lederhendler, National Institute of Mental Health. To be held Thursday, June 17, 2004, 1:00-2:00.

Student Workshop: *Student career development symposium: Selecting the right postdoctoral fellowship and getting the first position in academia or industry.* Organized by Gonzalez-Lima, E; Gonzalez-Lima, F; Gerlai, R. Department of Psychology, University of Texas at Austin; Department of Psychology and the Pacific Biomedical Research Center, University of Hawaii, Honolulu. The symposium is intended for the student who is thinking about making decisions as to the direction of his or her future career. To be held on Thursday, June 17, 2004, 2:00-4:00.

NOTE: All presentations, meetings, satellites, posters will be held in the **Big Pine/Conch/Duck Room** unless otherwise noted.
Presenting authors are indicated by **bold** type.

Tuesday, June 15:

8:30-6:00 **Satellite**: Defense Behavior – *Coral Reef Room*

Wednesday, June 16:

8:30-5:00 **Satellite**: Defense Behavior – *Coral Reef Room*

8:30-5:00 **Satellite**: Nicotine as a Therapeutic Agent – *Big Pine-Conch Room*

11:30-5:30 **Registration/Exhibitors Display** – *Fiesta Plantation Room/Patio*

6:00-7:00 **Opening Reception –** *West Lawn*

7:00-7:15 **Welcoming Remarks: Robert Blanchard**, The University of Hawaii

7:15-8:15 **Keynote Speaker**: **Michael Davis**, Emory University. Neural systems involved in fear, anxiety and extinction. *Introduction:* Robert Blanchard

Thursday, June 17:

7:30-8:30 **Continental Breakfast/Exhibitors Display –** *Fiesta Plantation Room/Patio*

8:30-10:30 **Symposium 1**: **Factors influencing the acceleration and delay of aging.** *Co-Chairs*: **Susan A. Farr** and **William Banks**, St. Louis University School of Medicine, St. Louis, MO, USA.

8:30 **William Banks** - St. Louis University School of Medicine. Delivery of antibodies and antisense across the blood-brain barrier: Treatment of cognitive impairments in an animal model of Alzheimer's disease.

8:54 **Tamas Horvath** - Yale University School of Medicine. Overlapping sites of action of ghrelin and uncoupling protein 2 in delaying aging.

9:18 **Linda Toth** - Southern Ilinois University School of Medicine. Sleep and aging in mice.

9:42 **Susan Farr** - St. Louis University. Treatments that reverse cognitive impairments in an animal model of Alzheimer's disease.

10:06 **Mark E. Bardgett** - Northern Kentucky University. Improving memory in rats with hippocampal damage: Implications for the aging brain.

10:30-10:45 **Refreshment Break/Exhibitors Display –** *Fiesta Plantation Room/Patio*

10:45-11:45 **Recognition of Local Scientist and Keynote Speaker**: **Paul Sanberg,** University of South Florida. Novel cell therapy approaches for brain repair. *Introduction*: **Brian McMillan**, East Carolina University

11:45-1:15 **Council Meeting** – *Sea Breeze Room*

1:00-2:00 **NIH Grant Workshop**: **Israel Lederhendler**, National Institute of Mental Health

2:00-4:00 **Student Workshop**: Student career development symposium: Selecting the right postdoctoral fellowship and getting the first position in academia or industry. *Chairs*: **Robert Gerlai**, The University of Hawaii; **Francisco Gonzalez-Lima**, The University of Texas.

4:00-5:30 **Student Travel Award Slide Blitz**: *Chair*: **Robert Gerlai**

5:30-7:30 **Poster Session 1** – *Grand Ballroom*

Refreshments

Learning and Memory I

1. EFFECTS OF THALAMIC INTRALAMINAR NUCLEI LESIONS ON ATTENTION AND WORKING MEMORY IN RATS. Newman, J.; **Burk, J.**
2. STRESS-INDUCED DISRUPTION OF BRAIN DEVELOPMENT AND LEARNING ABILITY IN DROSOPHILA. **Roberts, S**; de Belle, S; Wang, X.
3. AN NMDA RECEPTOR ANTAGONIST (CPP) AMELIORATES STRESS IMPAIRMENT OF MEMORY. **Park, C.**;Diamond, D.
4. SEX DIFFERENCES IN RATS' SUSCEPTIBILITY TO SHORT-TERM MEMORY IMPAIRMENT BY STRESS SUGGEST THAT MALES ARE THE FRAGILE SEX. **Woodson , J.**; Greaves, K.; Haynes, V.; Diamond, D.
5. † A PRIMATE MODEL OF THE COGNITIVE AND ELECTROPHYSIOLOGICAL EFFECTS OF ELECTROCONVULSIVE SHOCK (ECS) AND MAGNETIC SEIZURE THERAPY (MST). **Moscrip, T.D.**; Terrace, H.S.; Sackeim, H.A.; Lisanby, S.H.
6. THE ROLE OF GUSTATORY NEOCORTEX (GNC) IN THE EXTINCTION AND SPONTANEOUS RECOVERY OF A CONDITIONED TASTE AVERSION (CTA). **Mickley, G.A.**; Kenmuir, C.L.
7. PHOSPHORYLATION LEVELS OF THE NR1 SUBUNIT OF THE NMDA RECEPTOR INCREASE FOLLOWING CONDITIONED TASTE AVERSION ACQUISITION. **Lockwood, D.R.**; Fadool, D.A., Houpt, T.A.

Dietary Processes

8. † GALANIN, ALCOHOL AND DIETARY FAT: HOW ARE THEY RELATED?. **Leibowitz, S**; Carrillo, C; Avena, N; Johnson, D; Lewis, M; Rada, P; Karatayev, O; Hoebel B.
9. I.C.V. GALANIN (GAL) DECREASES FREE WATER INTAKE AND OPERANT REINFORCER EFFICACY IN WATER-RESTRICTED RATS. **Brewer, A**; Blackshear, A.;Robinson, J.

10. DIET SELECTION IMPROVES MORPHINE'S ANALGESIC ACTIONS IN RATS WITH STREPTOZOTOCIN-INDUCED DIABETES. **Leibovici, M**.; Foulds-Mathes, W.; Kanarek, R.B.
11. PHYSIOLOGICAL SIGNIFICANCE OF AN ENDOGENOUS SATIETY SUBSTANCE, 2-BUTEN 4-OLIDE (2-B4O) INCREASED IN FASTED STATE. **Oomura, Y.**; Aou, S.; Matsumoto, I.
12. A DOSE RESPONSE RELATIONSHIP BETWEEN ESTRADIOL VALERATE AND INTAKE OF CHOCOLATE CAKE MIX BATTER USING FEMALE RATS. **Reid, L.D.**; Boswell, K.J.; Caffalette, C.A.; Reid, M.L.
13. POSTCESSATION INCREASE IN FOOD INTAKE IN WOMEN. **Geiselman,P.J.**; Martin,P.D.; Copeland,A.L.; Ryan,D.H.; Businelle,M.S.; Kendzor,D.E.
14. VASOPRESSIN AND SUGAR ADDICTION. **Murphy, H. M.**; Wideman, C. H.
15. SERUM TRIGLYCERIDES INDUCE LEPTIN RESISTANCE AT THE BLOOD-BRAIN BARRIER. **Robinson, S.M.**; Banks, W.A.; Nakaoke, R.; Morley, J.E.
16. CHRONIC IL-1B IN MICE AS A MODEL OF CACHEXIA. **Joppa, M.A.**; Wilson, J.; Behan, J.; Foster A.C.; Gogas, K.R.; Markison, S.

Drugs and Behavior

17. MODULATION BY TYPE A AND TYPE B GABA RECEPTORS OF THE MOTOR RESPONSES PRODUCED BY D1-LIKE- AND/OR D2-LIKE DOPAMINERGIC AGONISTS IN THE RAT NUCLEUS ACCUMBENS**. Chevallier, K.**; Abraini J.H.
18. † PHENOTYPICAL CHARACTERIZATION OF TRANSGENIC MICE OVEREXPRESSING HUMAN WILDTYPE ALPHA-SYNUCLEIN. **Fleming, S.**; Levine, M.; Masliah, E.; Chesselet, M-F.
19. BLOCKADE OF NON-NMDA RECEPTORS PREVENTS NEUROTENSIN-INDUCED SENSITIZATION TO THE STIMULANT EFFECT OF AMPHETAMINE. **Rompré, P.-P.**; Serio, M.; Bauco, P.
20. DO SOCIAL PEERS ACT AS CUES IN THE ACQUISITION OF BEHAVIORAL ETHANOL TOLERANCE?. **Martin, J.**; Farmer-Dougan, V.; Siegel, S.
21. DOPAMINE D1 AND D2 RECEPTOR FAMILIES CONTRIBUTE TO THE COCAINE-INDUCED DISRUPTION OF PREPULSE INHIBITION IN MICE. **Doherty, JM**; Lehmann-Masten, V; Low, MJ; Geyer, MA.
22. EXERCISE POTENTIATES MORPHINE-INDUCED ANTINOCICEPTIVE TOLERANCE AND HYPERPHAGIA. **Mathes, W.F.**;Kanarek, R.B.
23. ENVIRONMENTAL FACTORS AND COCAINE PSEUDO-SENSITIZATION AND PSEUDO-TOLERANCE EFFECTS. **Carey, R.J.**
24. GALANTAMINE/NICOTINE COMBINATION AS A NOVEL STRATEGY TO IMPROVE NICOTINIC THERAPEUTICS. **Shytle RD**; Townsend K; Sun N; Zeng J; Newman M; Sanberg PR; and Tan J.
25. NICOTINE SENSITIZATION IN A RODENT MODEL OF PSYCHOSIS. **Perna, M.K.**; Smith, K.J.; Brown, R.W.
26. CHRONIC OLANZAPINE TREATMENT IN ADULTHOOD ELIMINATES COGNITIVE DEFICITS PRODUCED BY D2 RECEPTOR SUPERSENSITIZATION. **Thacker, S.**; Perna, M.; Smith K.; Kostrzewa, R.; Brown, R.
27. ACUTE ETICLOPRIDE TREATMENT ELIMINATES COGNITIVE DEFICITS PRODUCED BY NEONATAL QUINPIROLE TREATMENT. **Thompson, K.**; Click, I.; Best, R.; Thacker, S.; Brown, R.
28. EFFECT OF 5HT2C/2A RECEPTOR AGONISTS AND ANTAGONISTS ON ICSS RESPONDING IN RATS. **Martin, F.D.C.**; Mac Sweeney, C.P.; Marston, H.M.

29. REWARD-DEPENDENT INDUCTION OF FOS WITHIN LIMBIC BRAIN REGIONS. **Marcangione, C.**; Rompré, P-P.
30. CROSS-SENSITIZATION BETWEEN BRAIN STIMULATION REWARD AND AMPHETAMINE-INDUCED LOCOMOTION. **Boye, S.M.**; Grant, R.J.
31. THE ANABOLIC STEROID 17á- METHYLTESTOSTERONE MODULATES ANXIETY WHEN INFUSED INTO THE DORSOMEDIAL HYPOTHALAMUS ACCORDING TO SEX. **Rivera, J.C.**; Morales, L.; Vargas, N. M. and Jorge, J. C.
32. EXPOSURE TO AN ANABOLIC STEROID PREVENTS THE ANXIOLYTIC EFFECTS OF ETHANOL. **Rivera-Ramos, I**; Rundle, V; Rojas, Y, and Jorge, J.C.

Drugs and the Brain

33. ANABOLIC STEROID EFFECTS ON GABA IMMUNOREACTIVITY IN DISCRETE BRAIN NUCLEI. **Rundle-González, V**; Rivera-Ramos, I; Estrada-Barreto, J; Jorge, J.
34. FUNCTIONAL INTERACTIONS BETWEEN DOPAMINERGIC RECEPTORS AND GROUP II METABOTROPIC GLUTAMATERGIC RECEPTORS IN THE RAT NUCLEUS ACCUMBENS. **David, H.N.**; Abraini, J.H.
35. OREXIN-B EXCITES THE NEURONS IN THE PARAVENTRICULAR NUCLEUS OF THE THALAMUS OF RATS. **Sasaki, K.**; Ishibashi, M.; Takano, S.; Yanagida, H.; Takatsuna, M.; Nakajima, K.; Oomura, Y.
36. THE EFFECTS OF ACUTE PCP ADMINISTRATION ON THE P300 EVENT RELATED POTENTIAL IN RATS. Franck, L.; **Klipec, W.D.**; Schneider, B.; Maffin. L.
37. ANTICONVULSANT POTENTIAL OF AMILORIDE IN PENTYLENETETRAZOLE-INDUCED KINDLING IN MICE. **Ali, A.**; Vohora, D.; Ahmad, F.J.; Pillai, K.K.

Stress and Depression

38. STRAIN AND SEX-SPECIFIC EFFECTS OF UNPREDICTABLE CHRONIC MILD STRESS ON DEPRESSIVE BEHAVIOR IN MICE. **Mineur, Y.S.**; Crusio, W.E.
39. EXPOSURE TO CHRONIC UNPREDICTABLE STRESS REDUCES ESCAPE BEHAVIOR IN THE RAT. **Gouirand, A.G.**; Nilges, M.R.; Matuszewich, L.
40. DOSE-DEPENDENT EFFECT OF REPEATED CORTICOSTERONE ON DEPRESSION-LIKE BEHAVIOR IN MALE RATS. **Johnson, S.A.**; Stamp, J.A.; Kalynchuk, L.E.
41. EFFECTS OF DIFFERENT KINDS OF PARADOXAL SLEEP DEPRIVATION ON AGGRESSIVE BEHAVIOR INDUCED BY APOMORPHIN IN RATS. **Motta, S.C**; Calzavara, M. B.; Frussa Filho, R.; Leite, J. R.
42. SOCIAL BEHAVIOR IN A RESIDENT-INTRUDER TEST PREDICTS INDIVIDUAL VULNERABILITY TO STRESS-INDUCED ANHEDONIA IN C57BL/6N MICE. **Strekalova T**; Frynta D; Berger S; Henn F; Bartsch D.
43. DOES NEONATAL STRESS IMPACT CONTROL MOUSE BEHAVIOR IN A SPLIT LITTER DESIGN?. **Beard, N.**; Singletary, L.; Hohmann, C.F.
44. MATERNAL EXPERIENCE MODIFIES RESPONSIVENESS TO NOVEL STIMULI IN YOUNG AND SENESCENT LONG-EVANS RATS. **Torrey, N.**; Love, G., McNamara, I.; Brown, K.; Kinsley, C.H., & Lambert, K.G.
45. EFFECT OF MATERNAL CARE AND STAGE OF ESTRUS ON NEUROENDOCRINE RESPONSE TO ACUATE STRESS. **Cameron, N.M.**; Sharma, S.; Meaney, M.J.

46. MATERNAL SEPARATION INCREASES STRESS-INDUCED FOS EXPRESSION IN THE PVN OF BORDERLINE HYPERTENSIVE RATS. **Sanders, B.J.**; Anticevic, A.
47. EXTINCTION-INDUCED DESPAIR IN THE WATER MAZE: PROMISE OF A CONCEPTUAL AND EMPIRICAL MODEL OF HUMAN DEPRESSION. **Schulz, D.**; Topic, B.; De Souza Silva, M.A.; Huston, J.P.
48. MODELING DIFFERENTIAL RESPONSES TO ESTROGEN IN TWO RAT STRAINS. **Koss, W.A.**; Einat, H.*; Iqbal, S.A.; Manji, H.K.*; Rubinow, D.R.
49. SUBMISSIVE BEHAVIOR MEASURED IN RATS COMPETING FOR FOOD AS A MODEL OF DEPRESSION: STUDY WITH AUTOMATIC SCORING. **Crooke, J**; Pinhasov, A; Rosenthal, D; Brenneman, D; Malatynska E.
50. GAMMA SYNUCLEIN MRNA LEVELS DIFFER IN THE CORTEX OF SUBMISSIVE AND DOMINANT RATS SELECTED IN THE COMPETITION TEST. **Pinhasov, A**; Ilyin, SE; Crooke, J; Amato, FA; Vaidya AH; Rosenthal, D; Brenneman, DE; Malatynska, E.
51. COMPARISON OF RECORDINGS OF 22-kHz RAT CALLS BY DIRECT DIGITIZATION AND VIA BAT DETECTORS. Holland, G.; **Brudzynski, S.M.**

Friday, June 18:

7:30-8:30 **Continental Breakfast/Exhibitors Display –** *Fiesta Plantation Room/Patio*

8:30-10:30 **Symposium 2: Modeling abnormal brain and behavior development: When more is better.** *Co-Chairs*: **Mikhail V. Pletnikov**, Johns Hopkins University School of Medicine, and **Christine F. Hohmann**, Morgan State University, Baltimore, MD, USA.

8:30 **Christine F. Hohmann** - Morgan State University. Effects of neonatal serotonin depletions on cortical development and behavior: A mouse model for autism.

9:00 **Mary Blue** - Kennedy Krieger Institute. Genetic model for Rett Syndrome.

9:30 **Stephen Suomi** - National Institute of Child Health & Human Development. How gene-environment interactions can shape biobehavioral development in rhesus monkeys.

10:00 **Mikhail Pletnikov** - Johns Hopkins University School of Medicine. Viral models of neurodevelopmental injury.

10:30-10:45 **Refreshment Break/Exhibitors Display –** *Fiesta Plantation Room/Patio*

10:45-11:45 **Presidential Address: Robert Blanchard**. The organization and modeling of defensive behavior. *Introduction:* **Douglas Shytle**, University of South Florida

11:45-1:30 **Free time**

1:30-3:30 **Symposium 3**: **Estrogen: Old hormone, new tricks.** *Chair*: **C. Sue Carter**, University of Illinois at Chicago, Chicago, IL, USA.

1:30 **Emilie Rissman** - University of Virginia Charlottesville. The alpha and beta's of estrogen's actions in brain.

2:00 **Heather Patisaul** – Emory University. Soy and sex: The effect of dietary phytoestrogens on sex behavior.

2:30 **Margaret Altemus** - Cornell University. Chronic stress and anxiety: sex differences.

3:00 **Bruce Cushing** - University of Illinois at Chicago. Estrogen receptors and the regulation of male social behavior.

3:30-500 **Oral Session 1: Fear and Defense.** *Chair:* **Scott A. Heldt**, Yerkes Primate Research, Emory University.

3:30 LOCOMOTION IN A DARK OPEN FIELD COMPRISES "LOOPS" OF RETURNING TO RECENT PAST PLACES. Zadicario, P.; Zadicario, E.; Avni, E.; **Eilam, D**.

3:52 GLUCOCORTICOIDS IMPAIR FEAR MEMORY RETRIEVAL. **Cai, W.**; Greene, R.W.

4:14 ACTIVATION OF NADPH-DIAPHORASE POSITIVE NEURONS AFTER EXPOSURE TO A LIVE CAT. **Beijamini, V**; Guimaraes, FS.

4:36 THE SECURITY-MOTIVATION HYPOTHESIS OF OCD. **Szechtman, H.**; Woody, E.Z.

5:00-7:00 **Poster Session 2** – *Grand Ballroom*

Refreshments

Memory II

52. † ESTROGEN, BUT NOT ESTROGEN PLUS PROGESTERONE, ENHANCES MEMORY CONSOLIDATION IN AGED FEMALES. **Levy, L.**; Bennett, J.; Frick, K.
53. LONG-TERM CONTINUOUS, BUT NOT DAILY, ENRICHMENT REDUCES SPATIAL MEMORY DECLINE IN AGED MALE MICE. **Bennett, J.C.**; McRae, P.A.; Levy, L.J.; Frick, K.M.
54. † EFFECT OF CHRONIC OLANZAPINE ON SPATIAL MEMORY AND LOCOMOTOR ACTIVITY IN RATS WITH HIPPOCAMPAL DAMAGE. **McNutt, C.T.**; Gowdy, J.C.; O'Connell, S.M.; Bardgett, M.E.
55. CPEB NULL MICE DISPLAY ALTERED SPATIAL NAVIGATION REVERSAL LEARNING. **Terry, R.**; Stearns, N.; Yang, R.; Richter, J.; Berger-Sweeney, J.
56. DEFICIT OF DIFFERENT ASPECTS OF SPATIAL MEMORY IN TG2576 TRANSGENIC MICE AS A MODEL OF ALZHEIMER'S DISEASE. **Ognibene, E**; Middei, S; Daniele, S; Ghirardi, O; Caprioli, A; Laviola, G.

57. INDIVIDUAL DIFFERENCES IN WATER MAZE PERFORMANCE AND OPEN FIELD BEHAVIOR IN AGED AND ADULT RATS. **Topic, B.**; Jocham, G.; Kart, E.; Schulz, D.; De Souza Silva, M.A.; Huston, J.P.
58. α_7 NICOTINIC RECEPTOR ANTISENSE IMPAIRS PERFORMANCE IN THE MORRIS WATER MAZE AND DECREASES MLA BINDING. Curzon, P.; Anderson, D.J.; **Nikkel, A.L.**; Gopalakrishnan, M.; Decker, M.W.; Bitner, R.S.

Anxiety and Fear

59. NEUROTOXIC LESIONS OF THE DORSAL AND VENTRAL HIPPOCAMPUS IMPAIR ACQUISITION AND EXPRESSION OF TRACE CONDITIONED FEAR-POTENTIATED STARTLE. **Trivedi, M.A.**; Coover, G.D.
60. THE ROLE OF BOMBESIN-LIKE PEPTIDES IN FEAR-POTENTIATED STARTLE. **Mountney, C.**; Bedard, T.; Mennie, K.; Merali, Z.
61. THE ROLES OF GASTRIN-RELEASING PEPTIDE AND NEUROMEDIN B IN LEARNED FEAR AND ANXIETY. **Bédard, T.**, Mennie, K., Anisman, H., Merali, Z.
62. THE HABENULA COMPLEX MEDIATES EXPERIENCE-DEPENDENT REGULATION OF MONOAMINE SYSTEMS. **Heldt, S**; Ressler, K.
63. LINKS BETWEEN TEMPERAMENT DIMENSIONS AND BRAIN MONOAMINES IN THE RAT. **Hansen, S.**; Ray, J.; Waters, N.
64. V1aR EXPRESSION IN THE LATERAL SEPTUM IS NECESSARY AND SUFFICIENT FOR SOCIAL RECOGNITION IN MICE: A KNOCKOUT AND GENE REPLACEMENT STUDY. **Bielsky, I**.
65. ANXIETY LEVELS IN ADULT MICE THAT EXPERIENCED REPETITIVE ACUTE PAIN IN INFANCY VARY WITH AGE AND TESTING PARADIGM. **Mochinski, A**; Schellinck, H.
66. EFFECTS OF A MEDITATION PROCEDURE ASSOCIATED TO RESPIRATORY EXERCISES (SIDDHA SAMADHI YOGA- SSY) IN VOLUNTEERS WITH ANXIETY COMPLAINTS. **Kozasa, E.H.**; Krshnam L.I., Mohandas, S.; Desideri, A.V.; Rueda,A.D.; Silva,A.A.B.; Martins,I.; Leite,M.P.; Mendes,L.; Leite, J.R.

Anxiety II (Plus Maze)

67. EFFECTS OF AMYGDALAR OPIOID RECEPTORS IN ANXIETY-LIKE AND CONDITIONED FREEZING BEHAVIOR IN MALE RATS. **Burghardt, P.R.**; Wilson, M.A.
68. PREGNANCY AND CHANGES IN ANXIETY LEVELS IN WISTAR RATS. **Faturi, C. B.**; Teixeira-Silva ,F.; Leite, J. R.
69. CHRONIC UNPREDICTABLE STRESS INDUCES ANXIETY-LIKE BEHAVIORS IN THE DEFENSIVE BURYING PARADIGM, BUT NOT THE ELEVATED PLUS MAZE. **Karney, J.J.**; Klasinski, J.L.; Matuszewich, L.
70. TEMPORARY INACTIVATION OF THE DORSAL PERIAQUEDUCTAL GRAY MATTER REINSTATES THE ANXIOLYTIC-LIKE EFFECT OF MIDAZOLAM IN THE ELEVATED PLUS-MAZE TRIAL 2 IN RATS. **Carobrez, AP**; Bertoglio, LJ; Anzini, C; Lino-de-Oliveira, C.
71. DOES ORAL ADMINISTRATION OF GRIFFONIA SEED EXTRACT REDUCE VOLITIONAL ALCOHOL CONSUMPTION AND ANXIETY? **Parker, J.L.**; Caldwell, S.L.; Haven, K.E.; Hollen, S.G., James, N.L.; Williams, H.L.; McMillen, B.A.
72. ANXIOLYTIC ACTIVITY OF ERYTHRINA VELUTINA – AN ENDEMIC PLANT OF NORTHEASTERN BRAZIL. **Teixeira-Silva, F.**; Alves, M.F.S.; Marchioro, M.

73. MICROINFUSIONS OF 8-OH-DPAT INTO THE VENTRAL HIPPOCAMPUS PRODUCE ANXIETY IN THE ELEVATED PLUS-MAZE IN MICE. Fachini, G.; Reis, L.M.; Nunes-de-Souza, R.; **Canto-de-Souza, A.**
74. BEHAVIORAL RESPONSES FOLLOWED BY CHEMICAL STIMULATION OF THE MIDBRAIN PERIAQUEDUCTAL GRAY IN MICE. Carvalho-Netto, E.F.; **Nunes-de-Souza, R.L.**
75. ACTIVE/PASSIVE AVOIDANCE IN THE MOUSE ELEVATED PLUS-MAZE (EPM) AND OBSESSIVE COMPULSIVE DISORDER (OCD). Zhang, Z-J.; Schmid, S.; Schmidt, D.; Salomon, R; **Hewlett, W.**

Human Disease Models

76. † EARLY BEHAVIOURAL PHENOTYPES IN MOUSE MODELS OF HUNTINGTON'S DISEASE. **Hickey, M.A.**; Thomasian, S.; Gallant, K.; Levine, M.S.; Chesselet, M.-F.
77. EFFECTS OF L-TRYPTOPHAN DEPLETION AND LOADING ON RESPONSE DISINHIBITION IN HUMANS. **Jagar, AA**; Dougherty, DM; Addicott, M; and Trotter, D.
78. THE BRATTLEBORO RAT AS A MODEL FOR ATTENTION DEFICIT-HYPERACTIVITY DISORDER. **Danielson, JM**; Schmitt, MP; Stevens, KE.
79. † OXYTOCIN REVERSES DECREASED SOCIAL INTERACTION IN TWO ANIMAL MODELS OF SCHIZOPHRENIA. **Lee, P.R.**; Brady, D.; Shapiro, R.A.; Dorsa, D.M.; Koenig, J.I.
80. † 5-HT1A RECEPTOR KNOCKOUT MICE EXHIBIT HYPERSENSITIVITY TO CORTICOTROPIN RELEASING FACTOR EFFECTS ON LOCOMOTOR BUT NOT ACOUSTIC STARTLE BEHAVIORS. **Risbrough, V.**; Hen, R.; Geyer, M.
81. ORAL EFFICACY OF THE mGLU2/3 RECEPTOR AGONIST LY544344 IN ANIMAL MODELS OF PSYCHOSIS AND ANXIETY. **McKinzie, D.L.**; Knitowski K.M.; Hart, J.C.; Johnson, B.G.; Schoepp, D.D.
82. MEDIATION OF STRESS-INDUCED HYPERTHERMIA IN THE MOUSE BY IONOTROPIC GLUTAMATE RECEPTOR LIGANDS. **Rorick, L.M.**; Hart, J.C.; McKinzie, D.L.
83. ANXIOUS BEHAVIOR IN MECP2 MUTANT MICE, A MODEL FOR RETT SYNDROME. **Mwizerwa, O.**; Berger-Sweeney, J.
84. SYNAPTIC ALTERATIONS AND LOCOMOTOR IMPAIRMENTS IN AN MECP2-NULL MOUSE MODEL OF RETT SYNDROME. **Storer, E.S.**; Berger-Sweeney, J.

Defense

85. † PREDATOR ODORS AND THEIR AFFECTS ON OLFACTORY OSCILLATORY DYNAMICS. **Lowry, C.A.**; Kay, L.M.
86. † BEHAVIORAL DIFFERENCES IN FOUR STRAIN OF MICE IN THE RAT EXPOSURE TES (RET). **Yang, M.**; Agustsson, H.; Markham, C.; Blanchard, D.C.; Blanchard, R.J.
87. EFFECTS OF THE CRF ANTAGONIST SSR125543A ON AGGRESSIVE BEHAVIORS IN HAMSTERS. **Farrokhi, C.**; Blanchard, D.C.; Griebel, G.; Yang, M.; Markham, C.; Blanchard R.J.
88. † MODULATION OF PREDATORY ODOR PROCESSING FOLLOWING IBOTENIC ACID LESIONS TO THE DORSAL PREMAMMILLARY NUCLEUS. **Markham, C.M.**; Blanchard, R.J.; Cuyno, C.; Canteras, N.S.; and Blanchard, D.C.

89. ASSOCIATIVE AND NONASSOCIATE RESPONSES TO FERRET ODOR EXPOSURE IN RATS. **Masini, C.V.**; Sauer, S.; Campeau, S.
90. HOW DOES FOX ODOR INFLUENCE THE BEHAVIOR OF NAIVE RATS?. **Endres, T.**; Apfelbach, R.; Fendt, M.
91. THE NEURAL BASIS OF FOX ODOR-INDUCED FEAR BEHAVIOR. **Fendt, M.**; Endres, T.; Steiniger, B.
92. EFFECTS OF LESIONS TO THE DORSAL HIPPOCAMPUS ON DEFENSIVE BEHAVIORS. **Pentkowski, N.**; Cuyno, C.; Park, Y.; Blanchard, R.J.; Blanchard, D.C.

Drugs and Development

93. BEHAVIORAL AND GROWTH EFFECTS INDUCED BY LOW DOSE METHAMPHETAMINE ADMINISTRATION DURING THE NEONATAL PERIOD IN RATS. **Williams, M. T.**; Moran, M. S.; Vorhees , C. V.
94. † CHANGES IN CORTICOSTERONE AND MONOAMINES FOLLOWING EXPOSURE TO METHAMPHETAMINE AND MDMA FOR 5 OR 10 DAY PERIODS IN THE DEVELOPING RAT. **Schaefer, T L**; Able, J A; Skelton, M R; McCrea A E; Gudelsky; G A; Vorhees C V; Williams, M T.
95. PROZAC EXPOSURE DURING NEONATAL DEVELOPMENT ALTERS THE SEXUAL DIFFERENTIATION OF BEHAVIOR. **Fernandez, M.**; Fortis, Y.; Jorge, J.C.
96. THE EFFECTS OF IN-UTERO AND PRE-WEANLING EXPOSURE TO DEPLETED URANIUM ON NEUROBEHAVIORAL DEVELOPMENT OF THE RAT. **Rossi III, J.**; Bekkedal, M.; McInturf, S.; McDougle, F.; Lenger, A.; Allen, C.; Arfsten, D.
97. NEONATAL OXYTOCIN INCREASES ESTROGEN SENSITIVITY IN ADULT FEMALE RATS. **Perry, A.**; Cushing, B.

Cognition and Performance

98. FURTHER ANALYSYS OF FEMALE SEXUAL BEHAVIOR IN THE MULTIPLE PARTNER CHOICE TEST. **Ferreira-Nuño, A.**; Morales-Otal A.; Paredes-Guerrero, R.; Velázquez-Moctezuma, J.
99. ILLUMINATION LEVELS IMPACT BEHAVIORAL PERFORMANCE IN AN OPEN FIELD OBJECT RECOGNITION TASK. **Singletary, L.**; Hohmann, C.F.
100. INFLUENCES OF MATERNAL EXPERIENCE ON COGNITIVE, EMOTIONAL, AND SOCIAL COMPETITION RESPONSES ACROSS THE LIFESPAN OF LONG-EVANS RATS. **Love, G.**; McNamara, I.; Kinsley, C.; Lambert, K.
101. ACUTE EFFECTS OF SUCROSE AND NICOTINE ON COGNITIVE BEHAVIOR. D'Anci, K. E.; Schoemann, A. M.; Zablotsky, B.; Montalvan, C. R.; Taylor, H. A.; **Kanarek, R. B.**
102. SUGAR BINGEING ENHANCES DOPAMINE RELEASE IN THE ACCUMBENS, AND SHAM FEEDING ELIMINATES THE ACETYLCHOLINE SATIETY RESPONSE. **Avena, N.M.**; Rada, P.; Hoebel, B.G.
103. † LESIONS OF THE NUCLEUS ACCUMBENS DECREASE DISCOUNTING OF DELAYED BUT NOT PROBABILISTIC REWARDS. **Acheson, A.**; Farrar, A.M; Patak, M; Hausknecht, K.A.; Kieres, A.K.; de Wit, H.; Richards, J.B.

Saturday, June 19:

7:30-8:30 **Continental Breakfast/Exhibitors Display –** *Fiesta Plantation Room/Patio*

8:30-10:30 **Symposium 4: From complex phenotypes to genes: Finding the links in dependence and emotionality.** Co-Chairs: Markus Heilig, NIAAA, Bethesda, MD, USA/ Karolinska Institute, Stockholm, Sweden; & Rainer Spanagel, Institute of Mental Health, University of Heidelberg, Mannheim, Germany.

8:30 **Paula L. Hoffman** - University of Colorado Health Sciences Center. Microarray analysis identifies candidate genes and signaling pathways for acute functional ethanol tolerance.

9:00 **Lucinda G. Carr** - Indiana University School of Medicine. Complementary approaches identify the candidate gene alpha-Synuclein for alcohol preference in alcohol-preferring and alcohol-nonpreferring rats.

9:30 **Rainer Spanagel** - University of Heidelberg, Mannheim. The involvement of per genes in cocaine and alcohol addiction.

10:00 **Markus Heilig** - Karolinska Institute. Functional neuroanatomy and genetics of trait anxiety: Central role for the dorsomedial prefrontal cortex.

10:30-10:45 **Refreshment Break/Exhibitors Display –** *Fiesta Plantation Room/Patio*

10:45-11:45 **Keynote Speaker**: **George Koob,** The Scripps Research Institute. The dark side of addiction: Neuropharmacological disruption of the brain reward and stress systems. *Introduction*: **Markus Heilig**, Huddinge University Hospital

11:45-3:30 **Free time**

3:30-4:45 **Oral Session 2: Chemistry and Behavior.** *Chair:* **Paul A. Rushing**, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

3:30 A MEDIAL AMYGDALOID - VENTROMEDIAL HYPOTHALAMIC PATHWAY FOR FEEDING BEHAVIOR. Grundmann, S.; Pankey, E.; Cook, M.; Wood, A.; Rollins, B.; **King, B.**

3:45 ASSESSMENT OF THE POTENTIAL APPETITE SUPPRESSANT EFFECTS OF CANNABINOID CB1 ANTAGONISTS IN RATS. **McLaughlin, P.J.**; Swezey, L.; Winston, K.; Thotapally, R.; Liu, Q.; Makriyannis, A.; Salamone, J.D.

4:00 MODULATION OF ORAL WOUND HEALING: A ROLE FOR HPA ACTIVITY. **Engeland, C.G.**; Cacioppo, J.T.; Marucha P.T.

4:15 MDMA ('ECSTASY') AND METHAMPHETAMINE COMBINED: MORE TOXIC THAN EITHER DRUG ALONE? **McGregor, I.**; Clemens, K.; Van Nieuwenhuyzen, P.; Li, K.; Hunt, G.; Cornish, J.

4:30 THE EFFECT OF ENJOYMENT ON PERCEIVED DURATION: DOES WHAT YOU WATCH FIRST INFLUENCE WHAT YOU WATCH SECOND? **Wojtaszczyk, J. A.**; Carpenter, D. L.

4:45-5:30 **Business Meeting –** *Big Pine Room*

7:00-10:00 **Banquet –** *Big Pine/Conch/Duck/Fiesta Ballroom*
Presentation of Travel Awards

Sunday, June 20:

7:30-8:30 **Continental Breakfast/Exhibitors Display –** *Fiesta Plantation Room/Patio*

8:30-10:30 **Symposium 5: Introduction to behavioral measures of impulsivity for neuroscience.** Chair: Donald M. Dougherty, The University of Texas-Houston, Houston, TX, USA.

8:30 **Donald M. Dougherty** - University of Texas HSC-Houston. Methodologies and procedures used for the laboratory behavioral assessment of impulsivity.

9:00 **Dawn M. Marsh** - University of Texas HSC-Houston. Assessment of state-dependent modification of impulsivity.

9:30 **Charles W. Mathias** - University of Texas HSC-Houston. Assessment of trait-dependent aspects of behavioral impulsivity.

10:00 **Alan C. Swann** - University of Texas HSC-Houston. Trait and state impulsivity in bipolar disorder.

10:30-10:45 **Refreshment Break/Exhibitors Display –** *Fiesta Plantation Room/Patio*

10:45-12:15 **Oral Session 3: Development, Differences & Disease Models.** *Chair:* Mikhail Pletnikov, Johns Hopkins University School of Medicine.

10:45 INNATE BRAIN DIFFERENCES UNDERLYING THE VULNERABILITY TO DEPRESSION. Shumake, J.; Gonzalez-Pardo, H.; Conejo-Jimenez, N. M.; **Gonzalez-Lima, F.**

11:00 SOCIAL WITHDRAWAL, NEOFOBIA, AND STEREOTYPED BEHAVIOR IN DEVELOPING RATS EXPOSED TO NEONATAL ASPHYXIA. **Laviola G**, Adriani W, Rea M, Aloe L, Alleva E.

11:15 ACETYLCHOLINE AND ITS RELATED mRNAs EXPRESSION BY HIGH ACETALDEHYDE IN THE RAT FRONTAL CORTEX. **Jamal, M.**; Ameno S; Ameno, K.; Kumihashi, M.; Wang, W.; Uekita, I.; Kubota, T.; Ijiri, I.

11:30 BETA-CATENIN TRANSGENIC MICE SHOW ENDOGENOUS MOOD STABILIZER-LIKE BEHAVIORS. **Einat, H.**; Gould, T.D.; Eberhart, C.G.; Manji, H.K.

11:45 SLEEP RHYTHMICITY AND HOMEOSTASIS IN MICE WITH TARGETED DISRUPTION OF mPERIOD GENES. **Shiromani, P.J.**; Weaver, D.R.

12:00 ABNORMALLY EXCESSIVE CORTICAL DENDRITIC BRANCHING IN A KNOCKOUT MOUSE MODEL OF THE FRAGILE X MENTAL RETARDATION SYNDROME. **Mervis, R.F.**; Bachstetter, A.D.; Ather, T.; Maloney, T.; Cupples, A.; Toth, M.

12:15 **Adjourn**

Wednesday, June 16

7:15-8:15 Keynote Speaker: Michael Davis

FACILITATION OF FEAR EXTINCTION IN RATS AND EXPOSURE-BASED PSYCHOTHERAPY IN HUMANS WITH THE FUNCTIONAL NMDA AGONIST D-CYCLOSERINE. Davis, M. Department of Psychiatry, Emory University, Atlanta, GA 30322 Traumatic events lead to vivid fear memories that often come to mind (flashbacks), leading to distraction, loss of sleep, loss of concentration and distress. Exposure therapy (extinction) can be effective in reducing these fear memories but takes time and sometimes is only partially successful or of limited duration. Hence, treatments are needed to improve the efficacy of exposure therapy in post-traumatic stress disorders (PTSD) or phobias. Animal studies indicate that conditioned fear provides a model system to analyze traumatic fear conditioning. These studies show that extinction (repeated presentation of a fearful stimulus in the absence of the aversive event) models processes involved in exposure therapy in humans. Extinction does not erase fear memories but instead is an active learning process leading to associations that compete with or suppress fear memories. Animal studies show that extinction requires activation of a particular brain protein (the N-methyl-D-aspartate (NMDA) type glutamate receptor). Compounds that block this receptor block the development of extinction. NMDA receptor function can be enhanced by a compound called D-cycloserine and systemic administration of D-cycloserine dose-dependently facilitates the rate of extinction of conditioned fear. This requires concomitant exposure to the conditioned stimulus and involves NMDA receptors. This compound has been used in humans for other purposes and is well tolerated with no important side effects. In a clinical trial using a virtual reality environment in people with fear of heights, exposure to a virtual glass elevator was successful in reducing this phobia. When this exposure-based psychotherapy was combined with D-cycloserine there was a more rapid and more long lasting effect, as predicted from the rodent studies.

Thursday, June 17

7:15-8:15 Symposium 1: Factors influencing the acceleration and delay of aging

DELIVERY OF ANTIBODIES AND ANTISENSE ACROSS THE BLOOD-BRAIN-BARRIER: TREATMENT OF COGNITIVE IMPAIRMENTS IN AN ANIMAL MODEL OF ALZHEIMER'S DISEASE. Banks, W.A.C and Saint Louis University School of Medicine, St. Louis, MO 63106. Mouse models of Alzheimer's disease can be used to test potential therapeutics. The SAMP8 is a natural mutation that develops age-related cognitive impairments. By 12 mo of age, learning and memory impairments are severe in mice that are otherwise healthy. These mice overexpress amyloid precursor peptide and cognitive decline can be corrected by giving antibody or antisense directed against amyloid beta protein (ABP) directly into the brain. We have examined the ability of these two potential therapeutics to cross the blood-brain barrier (BBB), an important step in understanding their mechanisms of action. Antibody directed against ABP crossed the BBB slowly. The rate of passage at first equaled that of albumin, showing that the antibody likely enters the brain through the extracellular pathways. A later phase of entry was slower than for albumin, suggesting that an efflux system was operating against antibody accumulation in the CNS. A 42-mer phosphorothioate oligonucleotide antisense directed against ABP crossed the BBB rapidly and accumulated in the hippocampus. About 0.2-0.25% of an intravenously injected dose entered the brain by way of a saturable transport system and the antisense was retained for hours in stable form. 12 mo old SAMP8 mice with established cognitive impairments were treated with two doses of iv antisense given two weeks apart and tested two weeks after the last dose. Both learning and memory returned to normal. These studies show that therapeutics effective against ABP can be delivered across the BBB. Use of animal models also suggests that Alzheimer's disease may have a reversible component.

OVERLAPPING SITES OF ACTION OF GHRELIN AND UNCOUPLING PROTEIN 2 IN DELAYING AGING. Horvath, T.L.; Department of Ob/Gyn & Reproductive Sciences and Department of Neurobiology. Yale University School of Medicine, New Haven, CT 06520 Aging is associated with declining endocrine and brain functions. Little is known about the intracellular correlates of this process. We have been investigating the central nervous system effects of metabolism-associated mechanisms, including the role of mitochondrial uncoupling protein 2 (UCP2) and the gut hormone, ghrelin. UCP2 is expressed in distinct population of neurons in the hippocampus, hypothalamus, basal forebrain and brains stem. Overexpression of UCP2 proliferates mitochondria, elevates tissue ATP and ADP levels, diminishes free radical production and increases longevity. Ghrelin, a stomach-derived metabolic hormone, of which circulating levels diminish during aging, also affects neuronal functions in the hippocampus,

hypothalamus, basal forebrain and brain stem. Because of the overlapping brain sites that are targeted by ghrelin and UCP2 actions, and since the decline in circulating ghrelin levels during aging parallels increased free radical production of the brain, we have been studying the regulatory relationship between ghrelin and mitochondrial uncoupling. Our studies suggest that ghrelin directly affects UCP2 activity and that ghrelin and UCP2 synergistically enhance neuronal mechanisms that prolong lifespan without impaired brain functions.

SLEEP AND AGING IN MICE. Toth, L.A. Southern Illinois University School of Medicine, Springfield, IL 62794. USA Problems with sleep are a common feature of normal aging. Well-established age-related alterations in human sleep include frequent nighttime awakenings, increased activity during the normal sleep period, and a blunted circadian organization of sleep. These problems can be exacerbated in Alzheimer's patients, who may develop increased duration and frequency of nighttime awakenings and reduced time spent in slow-wave sleep (SWS) and rapid-eye-movement sleep (REMS). These changes in sleep impair cognitive performance, functionality, and quality of life, and may precipitate institutionalization of the elderly. Animal models of Alzheimer's disease capture many of the clinical features of disturbed sleep in aged humans. For example, mice that over-express the human mutant b-amyloid precursor protein develop age-related changes in spontaneous locomotor activity, the amounts of SWS and REMS, and the circadian organization of sleep and activity. Similarly, senescence-accelerated mice of the P8 sub-line (SAMP8) show age-related alterations in spontaneous activity and in the circadian organization of activity, as well as fragmentation of sleep. These animals provide an avenue for identifying the causes of and therapies for age-related disturbances in sleep and circadian control. Supported by NIH grants NS-40220, HL70522, and RR17543.

TREATMENTS THAT REVERSE COGNITIVE IMPAIRMENTS IN AN ANIMAL MODEL OF ALZHEIMER'S DISEASE. FARR, S.A.VMAC and Saint Louis University School of Medicine, St. Louis, MO 63106 Alzheimer's disease is a devastating age-related disorder that results in cognitive impairment. Mouse models reflecting this impairment, such as the SAMP8, can be used to test potential therapeutics. A natural mutation that develops age-related cognitive impairments, which corresponds to elevated amyloid beta protein (ABP) levels in the brain. Learning and memory impairments are severe in mice that are otherwise healthy by 12 months of age. We have examined several treatments in SAMP8 mice that reversed learning and memory impairments seen at 12 months of age. Our first set treatments involved decreasing ABP. Antibodies to ABP improve learning and memory in SAMP8 mice and return dose response curves for memory enhancing compounds to that of a young unimpaired SAMP8 mouse. ICV administration of antibody for ABP given 24 hours prior training and up to two weeks post injection improved learning and memory and returned the sensitivity to both the cholinergic and glutamatergic compound to that of a young SAMP8 mouse. Examination of antibody administration on acetylcholine levels using microdialysis revealed that within 30 minutes post injection there was over a 100% increase in acetylcholine levels compared to preinjection levels. Antisense oligonucleotide directed at the ABP region of the APP peptide, which blocks the future production of ABP, was also able to reversed memory impairment. Antioxidants are another potential treatment for age-related disorders. We found that alpha lipoic acid, a potent antioxidant, was able to reverse cognitive impairments and reduce measures of oxidative stress. Together these findings indicate dementia in Alzheimer's may be reversible. Supported by VA

IMPROVING MEMORY IN RATS WITH HIPPOCAMPAL DAMAGE: IMPLICATIONS FOR THE AGING BRAIN. Mark E. Bardgett Department of Psychology, Northern Kentucky University, Highland Heights, KY 41099. Some aspects of learning and memory are adversely affected by aging, and some age-related cognitive decrements have been correlated with degenerative changes in the hippocampus. Moreover, the memory loss found in disorders of aging, such as Alzheimer's disease, has been clearly linked to reduced hippocampal volume. Our laboratory has been interested in identifying treatment strategies that may improve or reverse memory loss in adult rats and mice with hippocampal damage. The majority of our work has focused on atypical antipsychotic drugs, which reportedly have cognitive-enhancing effects in some human clinical disorders and are often used in the treatment of Alzheimer's disease. To date, we have assayed the effects of clozapine, risperidone, and olanzapine on delayed spatial alternation memory in rats with hippocampal damage. Our studies have found that the memory loss produced by hippocampal damage is modestly improved after chronic treatment with risperidone. This finding suggests that the memory loss produced by hippocampal damage may be sensitive to treatment intervention. We hope that continued work with our animal model will reveal even better treatments for the memory loss associated with hippocampal damage. In doing so, our research may advance the treatment of memory disorders associated with aging and, perhaps, memory loss observed in normal aging. Supported by NIH Grant Number P20 RR 16481 from the National Center for Research Resources.

10:45-11:45 Keynote Speaker: Paul Sanberg

NOVEL CELL THERAPY APPROACHES FOR BRAIN REPAIR. Paul R. Sanberg, Ph.D., D.Sc. – Associate Vice President and Distinguished University Professor, Center of Excellence for Aging and Brain Repair – University of South Florida College of Medicine, 12901 Bruce B. Downs Boulevard, MDC-78 Tampa, FL 33612.

Cell Therapy is a promising approach to the treatment of neurodegenerative diseases and brain injury that has been shown to be efficacious in many animal models. However, the use of fetal tissue limits the acceptability and wide spread application of the technique. This talk will discuss possible alternative cell sources that may be used to repair the brain and spinal cord, with a focus on adult stem and progenitor cells, including hNT Neurons, bone marrow and umbilical cord blood derived stem cells. Preclinical and clinical results in Parkinson's and stroke will be highlighted.

2:00-4:00 Student Workshop

STUDENT CAREER DEVELOPMENT SYMPOSIUM: SELECTING THE RIGHT POSTDOCTORAL FELLOWSHIP AND GETTING THE FIRST POSITION IN ACADEMIA OR INDUSTRY. Gonzalez-Lima, E; Gonzalez-Lima, F; Gerlai, R. Department of Psychology, University of Texas at Austin; Department of Psychology and the Pacific Biomedical Research Center, University of Hawaii, Honolulu The symposium is intended for the student who is thinking about making decisions as to the direction of his or her future career. Career decisions are complex questions but luckily students of behavioral neuroscience nowadays have multiple options. Nevertheless, the sooner one starts thinking about what the ideal position should be and how it could be obtained the more well prepared the student will be when the time comes to make the big leap. The symposium will discuss such important questions as selecting the right postdoctoral program, choosing a faculty position, selecting the University, the Department and the mentor, or colleagues. In addition the question of whether one should choose an academic or industry position and the benefits and disadvantages of each will be discussed. Multiple speakers will discuss how to choose and search for a training program, how to make initial contacts and make site visits, explore availability of resources and financial support, how to develop a realistic research plan. In addition, the importance of developing professional skills will be stressed, including writing and publishing papers, making effective oral presentations, applying for grants (such as the Individual National Research Service Awards and K01 Career Awards), mentoring, and preparing a teaching/research portfolio. Upon completion of the postdoctoral fellowship, the weight of the decision is perhaps even heavier. Where should you start your first professional appointment? Criteria for selecting a position will be discussed, including opportunities for tenure, resources to support your research, institutional prestige, quality of the trainees, and opportunities to improve your career through networking with colleagues. Criteria for evaluating an offer will be also discussed, including commitment of department to career development of junior faculty, start-up funds and resources to support professional activities. Appropriate expectations regarding time for teaching, research, administration and service, availability of mentors to support the development of professional skills and provide understanding of the criteria for promotion and tenure, availability of a larger community with similar interests, access to trainees at all levels, and integrity of the department chair will all be touched upon. Lastly the question of whether to select an academic or industry position will be analyzed. The pros and cons of academic vs. industry employment will be discussed with particular focus on academic freedom vs. company policy, having to write grants and to teach vs. being able to focus on research. Stability (tenure) in Academia vs. higher pay but perhaps riskier (less stable) positions in Industry will be compared. Long term prospects in both with regard to one's own aspirations and goals will be discussed. The presentations will be followed by open interactive discussions between the speakers and the audience.

5:30-7:30 Poster Session 1

Learning and Memory I

1. EFFECTS OF THALAMIC INTRALAMINAR NUCLEI LESIONS ON ATTENTION AND WORKING MEMORY IN RATS. Newman LA, Burk JA. Effects of thalamic intralaminar lesions on attention and working memory in rats. Dept of Psychology, College of William & Mary, Williamsburg VA 23187. In rats, lesions of the thalamic intralaminar nuclei disrupt performance in several working memory tasks that involve processing different types of information. The extent to which these lesions disrupt attention, and that attentional deficits can account for the mnemonic impairments, remains unclear. In the present experiment, rats were trained in a two-lever sustained attention task that required discrimination between the presentation of brief visual signals (500, 100, or 25 msec) and no signal. Upon reaching stable performance, rats were assigned to receive infusions of 150mM NMDA into the thalamic intralaminar nuclei (N=11) or sham surgery (N=10). Rats were then trained in the same task as immediately prior to surgery. A flashing houselight was presented for one session as a visual distractor and then a retention interval (1", 3", or 10") was incorporated after a signal or a nonsignal to test the effects of increasing the working memory requirement. On the attention task following surgery and during the distractor session, the performance of lesioned animals did not differ significantly from sham-lesioned rats. When a retention interval was included, lesioned animals demonstrated significant deficits in detecting signals compared with sham-lesioned animals. The present data support the hypothesis that the thalamic intralaminar nuclei are necessary for normal mnemonic processing but lesions of this region do not affect attention. These data are consistent with the idea that

the thalamic intralaminar nuclei are important for retrieval rather than encoding relevant sensory inputs. Supported by a Young Investigator Award from NARSAD to JAB.

2. STRESS-INDUCED DISRUPTION OF BRAIN DEVELOPMENT AND LEARNING ABILITY IN *DROSOPHILA.* Roberts, S.P.; de Belle, J.S.; Wang, X. Dept. of Biological Sciences, University of Nevada, Las Vegas, NV 89154-4004 USA. Environmental stress exposure (nutritive, chemical, electromagnetic and thermal) has been shown to disrupt CNS development in every model system studied to date, including humans. However, few studies have linked environmental stress to critical targets in brain development and their consequences for behavioral domains. Here we address this issue by examining the effects of thermal and chemical stress on development of the *Drosophila melanogaster* mushroom body (MB), a highly conserved paired neuropil structure in the insect brain that is important for associative learning. *Drosophila* MB development is sensitive to exposure to the cytostatic drug hydroxyurea, which leads to a profound loss of MB volume in adult flies. These MB-less flies respond to odors but are unable to form memories of odors paired with electric shocks. When 25 °C-reared *D. melanogaster* are exposed daily to a brief heat shock (39.5 °C for 40 min) throughout larval and pupal development, MB volume is reduced by roughly 40%. However, the central complex (a central brain structure involved in motor control), wings and legs show little or no reduction in size relative to control flies reared at a constant 25 °C. Mutants with similarly reduced MB size are learning impaired, and the effects of thermal stress on learning and behavioral plasticity are being investigated.

3. AN NMDA RECEPTOR ANTAGONIST (CPP), AMELIORATES STRESS IMPAIRMENT OF MEMORY. Park, C.R.; Diamond, D.M. Department of Psychology, University of South Florida & Research Service, James A. Haley Veterans Hospital, Tampa, FL 33612 USA We have previously shown that psychological stress (exposure to a cat) can impair spatial memory performance in the radial-arm water maze. In order to determine the mechanism of the impairment we tested the effect of an NMDA receptor antagonist (CPP, 10 mg/kg, i.p.) on the cat stress-induced impairment. Using a single-day training procedure, we found that both cat stress and CPP impair the retrieval of a 24-hr. spatial memory. Using a long-duration (4 days) training procedure, we found that CPP will ameliorate the cat stress-induced retrieval deficit, but will not impair by itself. Given even longer training parameters (11 days of training), neither CPP nor cat stress will impair retrieval. These results suggest that the impairment of spatial memory retrieval by cat stress is mediated by NMDA receptor activation. Further, as the memory of a spatial location is reorganized into reference memory, it eventually loses sensitivity to NMDA receptor activation.

4. SEX DIFFERENCES IN RATS' SUSCEPTABILITY TO SHORT-TERM MEMORY IMPAIRMENT BY STRESS SUGGEST THAT MALES ARE THE FRAGILE SEX J.C. Woodson 1,3*; K. Greaves 1; V.F. Haynes 4; D.M. Diamond 1,2,3 1. Psychology; 2. Pharmacology, University of South Florida, Tampa, FL, USA; 3. Medical Research, VA Hospital, Tampa, FL, USA; 4. Psychology, Youngstown State University, Youngstown, OH, USA; 5. University of Tampa, Tampa, FL USA. In our spatial memory/stress testing paradigm, rats are trained to learn and then to remember the location of a hidden platform in a radial-arm modified water maze. We have shown previously that rats exhibit a fear-specific impairment of recent, but not long-term (presumably consolidated), memory for the platform location (Learning & Memory, 10:326-336, 2003). We obtained similar findings when the stressor was either inhibitory avoidance (IA) training, or re-exposure to the IA context as much as 1 year after the shock occurred. Here, we have compared the effects of IA training and context re-exposure on water maze spatial memory in adult male and female rats. At three months of age, gonadally intact male and female Sprague-Dawley rats were trained in the water maze to learn the location of a hidden platform. Then they were given inhibitory (shock) avoidance (IA) conditioning. One hour later, the rats were returned to the water maze and their memory of the location of the hidden platform was tested. Male and female rats both exhibited excellent spatial memory under control conditions, i.e., when they spent the 60 min delay period in their home cages. Male rats' spatial memory was impaired when they learned the platform location and then were given either IA training (with a brief, 0.6 ma pawshock) or when they were re-exposed to the IA context (without shock) during the delay period. Female rats' spatial memory was not significantly affected by IA training or re-exposure to the shock context. During IA re-exposure all rats exhibited a strong avoidance of the original shock compartment, thereby indicating that their emotional memory of the shock experience was intact. These findings suggest that males may be more vulnerable to interference of hippocampal functioning under stressful conditions. Support contributed by VA Merit Review Award.

5. A PRIMATE MODEL OF THE COGNITIVE AND ELECTROPHYSIOLOGICAL EFFECTS OF ELECTROCONVULSIVE SHOCK (ECS) AND MAGNETIC SEIZURE THERAPY (MST) T.D. Moscrip 1,3; H.S. Terrace 1,2; H.A. Sackeim 2,3; S.H. Lisanby 2,3 1.Psychology, Columbia Univ, New York, NY, USA 2.Psychiatry, Columbia Univ College of Physicians and Surgeons, New York, NY, USA 3.Biological Psychiatry, New York State Psychiatric Institute, New York, NY, USA Electroconvulsive therapy (ECT), the most effective treatment for major depression, produces anterograde and retrograde amnesia. Like ECT, magnetic seizure therapy (MST) induces generalized seizures, but stimulates a more localized region of superficial cortex and may be

associated with less severe cognitive side effects. This study assessed the sensitivity of a nonhuman primate model to the amnesic effects of convulsive therapy and measured the electrophysiological characteristics of electrically- vs. magnetically-induced seizures. Rhesus macaques were trained on 3 tasks of increasing complexity: a long-term memory task, an anterograde learning & memory task, and a combined anterograde & retrograde task where learning and memory were evaluated for new & previously trained 3-item lists. Baseline measures of cognition were obtained 2 wks prior to testing. A within-subject cross-over design was used, consisting of daily ECS or MST treatments for 5 wks, followed by a 5-wk recovery period. Monkeys received IV methohexital in their homecages via voluntary venipuncture and were trained and tested twice daily, with a 3-hr retention interval between sessions. Monkeys performed more accurately on all tasks following MST, as compared to ECS. This effect was most marked for the short-term memory of a variable target and new list testing. Intracerebral EEG recordings revealed that ECS resulted in greater global power and induced voltage compared to that of MST. This effect was most apparent in the hippocampal region. These preliminary findings suggest that MST and ECS result in different profiles of acute cognitive impairment and electrophysiology.

6. THE ROLE OF GUSTATORY NEOCORTEX (GNC) IN THE EXTINCTION AND SPONTANEOUS RECOVERY OF A CONDITIONED TASTE AVERSION (CTA). Mickley, G.A.; Kenmuir, C.L. Neuroscience Program and Department of Psychology. Baldwin-Wallace College, Berea, OH 44017-2088 USA. While substantial advances have been made in discovering how the brain learns and remembers, less is known about how the brain mediates extinction of conditioned behaviors or changes during spontaneous recovery (SR). These topics are not only relevant to normal brain functioning but also speak to pathologies in which painful memories do not wane but are evoked time and again (e.g., Post-traumatic stress disorder; PTSD). CTAs may be acquired when an animal consumes a novel taste (conditioned stimulus; CS) and then experiences the symptoms of poisoning (unconditioned stimulus; US). When later given a choice between the CS and some more-familiar gustatory stimulus (typically water), the animal will avoid the taste that it previously associated with malaise. Extinction of a CTA is observed following repeated, nonreinforced exposures to the CS and represents itself as a resumption of eating/drinking the once-avoided tastant. SR of a CTA (a revival of the taste avoidance) occurs after a latency period in which the CS is not presented. The neuronal pathway that subserves CTA acquisition is well known and the GNC plays a primary role in the mediation of both the acquisition and extinction of this memory. This study investigated changes in GNC functioning during acquisition, extinction and spontaneous recovery of a CTA. Brain c-Fos protein expression was analyzed in fluid-deprived rats that had acquired a CTA [3 pairings of 0.3% oral saccharin (SAC) and 81mg/kg i.p. Lithium Chloride (LiCl)] followed by extinction training (i.e., subsequent non-reinforced SAC exposures) resulting in 90% reacceptance of SAC. Other animals were extinguished but spontaneously recovered the CTA upon exposure to SAC following a 15-, 30-, 45- or 60-day recovery period of water drinking. Rats were sacrificed on the final day of SAC exposure and GNC c-Fos protein expression was evaluated. SR of the CTA depended on both the time to meet the extinction criterion and the length of the recovery period. Animals allowed 30- or 60-day recovery periods exhibited a significant SR. The numbers of c-Fos-labeled neurons in GNC was low following CTA acquisition but increased dramatically as rats fully extinguished the aversion. However, a significant decline in c-Fos expression accompanied SR of the CTA. These data elucidate the behavioral parameters required to observe the SR of a CTA. Further, the immunohistochemical measurements suggest the dynamic nature of GNC activity during acquisition, extinction and SR of a CTA and further reinforce an important role for these cortical neurons in the reorganization of learned information. Supported by NIMH.

7. PHOSPHORYLATION LEVELS OF THE NR1 SUBUNIT OF THE NMDA RECEPTOR INCREASE FOLLOWING CONDITIONED TASTE AVERSION ACQUISITION Lockwood, D.R.; Fadool, D.A.; Houpt, T.A. Dept. of Biological Science, The Florida State University, Tallahassee, FL 32306-4340 USA. Many cellular processes are regulated by changes in phosphorylation state, including gene expression and synaptic plasticity, both thought to underlie learning. Evidence exists which suggests that alterations in phosphorylation state of the NMDA receptor may be significant in mediating conditioned taste aversion (CTA) learning. In order to better understand the role of this type of regulation, we characterized changes in the phosphorylation state of the NR1 subunit of the NMDA receptor during CTA acquisition. Rats implanted with intraoral catheters were conditioned with an infusion of 5% sucrose (6 ml over 6 min) (conditioned stimulus; CS) followed by i.p. injections of LiCl (0.15 M, 12 ml/kg) (unconditioned stimulus; US) 15 minutes after the CS. The rats were sacrificed 15 minutes after the injections and the amygdalas removed and processed for western blotting. Protein bands corresponding to the C-terminus of unphosphorylated NR1 or full length NR1 phosphorylated at serine residue 897 (S897) or serine 896 (S896) were detected using phospho-specific antibodies. Preliminary data show an increase in phosphorylation 15 minutes post-treatment at S896 following the CS and US stimuli alone, as well as a single pairing of CS+US, compared to untreated rats. Phosphorylation was increased at S897 following CS, but decreased following US alone and CS+US, possibly due to an increase in phosphatase activity. Subsequent experiments will examine the dephosphorylation of these residues, in order to determine if a critical role for protein phosphatase 1 exists during CTA acquisition.

Dietary Processes

8. GALANIN, ALCOHOL AND DIETARY FAT: HOW ARE THEY RELATED? Leibowitz, S.F. [1], Carrillo, C. [2], Avena, N.M.[2], Johnson, D.F.[2], Lewis, M.J.[2], Rada, P.[3], Karatayev, O.[1] and Hoebel, B.G.[2]. [1] Laboratory of Behavioral Neurobiology, Rockefeller Univ, NY, NY, 10021 USA.; [2] Dept of Psychology, Princeton Univ, Princeton, NJ, 08544, USA; [3] Laboratory of Behavioral Physiology, Univ. of Los Andes, Merida, Venezuela. It is known that galanin (GAL) injection into the paraventricular nucleus (PVN) can stimulate feeding, most potently on a high-fat diet, and that intake of a high-fat diet stimulates GAL expression. New studies demonstrate that ingestion of ethanol stimulates GAL mRNA in the PVN. Experiments were designed to determine whether GAL injection can increase the drinking of ethanol and whether a positive relationship exists between fat and ethanol ingestion. In two separate studies, ethanol-experienced rats given access to 4-7% ethanol and water for 12 hr/day were infused with GAL or Ringer. Compared to vehicle, infusion of GAL (1.0 and 3.0 nmole) into the 3rd ventricle or of GAL (0.5 and 1.0 nmole) into the PVN significantly increased ethanol intake, in a dose-dependent manner and in the presence of food and water. PVN injection of the GAL antagonist, M40 (0.5 nmole), reduced ethanol intake. A positive relationship between fat and ethanol intake was demonstrated by two additional experiments in rats trained to consume 7-9% ethanol while on lab chow. Ethanol intake was significantly higher in rats previously shown to exhibit hyperphagia on a chronic high-fat diet compared to normophagic rats (2.21 vs 1.19 g/kg/day, $p<0.02$) and in rats given a high-fat meal compared to low-fat meal (0.97 vs 0.45 g/kg/4hr, $p<0.01$). These findings suggest a role for GAL in a positive relationship between dietary fat and ethanol consumption. Supported by: USPHS grants AA012882 and MH 43422.

9. I.C.V. GALANIN (GAL) DECREASES FREE WATER INTAKE AND OPERANT REINFORCER EFFICACY IN WATER-RESTRICTED RATS. Brewer, A.; Blackshear, A.L.; Robinson, J.K. Dept. of Psychology. Stony Brook University, Stony Brook NY 11794 USA. The neuropeptide Gal reliably stimulates feeding when administered i.c.v. or intrahypothalamically in the rat. Gal also produces delay-independent accuracy deficits and reduces trials per session in the operant delayed nonmatch-to-position (DNMTP) task. This procedure employs water reinforcers to maintain behavior. This decrease in trials might reflect a change in the efficacy of the water reward. One previous report which examined Gal effects on drinking (Kyrkouli et al., 1990, Peptides, 11, 995) showed no change in the low proportion of time spent drinking compared to other activities in a one hour test session following hypothalamic Gal infusion (0.32 µgs). Therefore, the present study examined the effects of Gal (0.5-20.0 µg/5 µl i.c.v.) on several tests: (1) free water consumption during a 10 min test session in 23.5 hour water-restricted rats, (2) open field exploration, (3) an operant progressive ratio (PR) schedule, a test used to assess reinforcer strength, and (4) a DNMTP task in which periods of pre-session water access were allowed in order to reduce reward strength. A Gal-induced decrease in water consumption in the free access test was observed at the 20 µg dose, but no significant alterations in open field behavior. A decrease in responses and rewards was also observed in the PR schedule at the 10 and 20 µg doses. Pre-session water reduced the number of trials/session in the DNMTP but did not reduce accuracy. This study is the first to suggest that Gal may play a role in regulating water intake and reinforcement, and that DNMTP choice accuracy deficits cannot be attributed to a Gal-induced change in reinforcer efficacy.

10. DIET SELECTION IMPROVES MORPHINE'S ANALGESIC ACTIONS IN RATS WITH STREPTOZOTOCIN-INDUCED DIABETES. Leibovici, M.; Foulds-Mathes, W.; Kanarek, R.B. Dept. of Psychology, Tufts University, Medford, MA 02155 USA Both diabetic patients and animals with experimentally-induced diabetes often suffer from neuropathic pain. Additionally, diabetes is frequently associated with a reduction the pain relieving properties of opiate drugs. Previous work showed that rats allowed to self-select their diet from separate sources of protein, fat and carbohydrate displayed milder symptoms of diabetes after injections of the diabetogenic drug, streptozotocin (STZ) than rats given a single laboratory diet. Two experiments were conducted to determine if permitting STZ-diabetic rats to select their diet would also 1) reduce the severity of diabetic neuropathy and 2) increase sensitivity to the analgesic properties of morphine. Pain was measured using the hot-water tail withdrawal test. In Experiment 1, rats maintained on a diet selection regime for 4 weeks before and after STZ administration (45 mg/kg i.p.) developed less severe symptoms of diabetes (e.g. lower blood glucose levels); had higher baseline levels of pain tolerance, and were more sensitive to the pain relieving actions of morphine than diabetic rats fed either chow or a composite diet. In Experiment 2, rats that were fed a composite diet for 4 weeks prior to STZ injections, and only given the self-selection diet after STZ administration did become diabetic and show attenuated morphine induced antinociception. The results of these experiments show that pre-exposure to dietary self selection can lessen symptoms of diabetes and improve responsiveness to morphine-induced analgesia in diabetic rats

11. PHYSIOLOGICAL SIGNIFICANCE OF AN ENDOGENOUS SATIETY SUBSTANCE, 2-BUTEN 4-OLIDE I2-B4O) INCREASED IN FASTED STATE. Oomura, Y.; Aou, S.; Matsumoto, I. Department of Integrated Physiology, Faculty of Medicine, Kyushu University, Fukuoka, Department of Brain Science, Kyushu Institute of Technology, Kitakyushu and Department of Physiology, Faculty of Medicine, Nagasaki University, Nagasaki,

Japan. A sugar acid, 2-B4O has been found to increase from 3.5 to 13 in rat serum ìM at 36 h after food deprivation. Injections of 2-B4O (2.5 ìM) into rat III cerebral ventricle suppress food intake and single neuronal activity in the lateral hypothalamic area (LHA, feeding center). 2-B4O hyperpolarizes glucose-sensitive neurons in the LHA via Na-K pump activation, while depolarizes the glucoreceptor neurons in the ventromedial nucleus, satiety center, via closure of ATP-sensitive K channels. The plasma levels of glucose, corticosterone, and catecholamines, and firing rate in both parvocellular neurons in the paraventricular nucleus and sympathetic efferent nerves all increase 2-B4O intravenous injection, indicating activation of the hypothalamo-pituitary-adrenal axis. A 2-B4O iv injection facilitates emotional and spatial learning and memory, and pretreatment of anti-acidic fibroblast growth factor (aFGF) antibody icv eliminates these effects. aFGF is released from ependymal cells in the III cerebral ventricle in response to the glucose increase in CSF induced by 2-B4O iv injection. 2-B4O suppresses the clinical symptoms of experimental allergic encephalomyelitis (EAE) in Lewis rats, a model for human multiple sclerosis. These results indicate that 2-B4O is not only a powerful satiety substance, but also effective as an activator of the hypothalamo-pituitary-adrenal axis and sympathetic efferent outflow, and as a memory facilitation and a suppressant of autoimmune function.

12. A DOSE RESPONSE RELATIONSHIP BETWEEN ESTRADIOL VALERATE AND INTAKE OF CHOCOLATE CAKE MIX BATTER USING FEMALE RATS. REID, L.D.; BOSWELL, K.J.; CAFFALETTE, C.A.; REID, M.L. Laboratory for Psychopharmacology. Rensselaer Polytechinic Institute, Troy, NY and Siena College, Loudonville, NY, USA. Female, Sprague-Dawley rats were given the opportunity to take a batter made from chocolate cake mix for 24 hr a day for 8 days along with their usual food and water. Six days before the opportunity, 6 groups, 8 females a group, were given one of 5 doses of estradiol valerate (EV) or placebo. EV releases estradiol slowly. The doses of EV were 1.5, 0.75, 0.375, 0.19, and 0.09 mg/kg given intramuscularly in a carrier of sesame oil. Injections of oil served as a placebo. Subjects take large amounts of batter under the influence of placebo-injections, often 75-80 g/kg a day with some intakes even exceeding 100 g/kg. Doses of EV of 0.19 mg/kg and above reliably increased intakes about 25%. Previous research indicated that estradiol decreased appetite. The procedural difference concerning when injections are programmed, in relation to the first opportunity to take a novel palatable ingesta, can account for the difference in whether estradiol is an appetite suppressant or an appetite enhancer. It is clear that pharmacological doses of estradiol can enhance appetite for palatable ingesta.

13. POSTCESSATION INCREASE IN FOOD INTAKE IN WOMEN. Geiselman,P.J.; Martin,P.D.; Copeland,A.L.; Ryan,D.H; Businelle,M.S.; Kendzor,D.E. Pennington Biomedical Research Center/LSU, Baton Rouge,LA 70808 USA. Women get more weight control benefits from smoking and suffer more postcessation weight gain than do men. Further, one of the primary nicotine withdrawal symptoms differentiating men and women postcessation is increased appetite in women. Although significantly increased food intake has been implicated as the principal factor in postcessation weight gain, the issue of effects of smoking cessation on specific macronutrient intake is not yet resolved. In the past, studies in the smoking cessation literature have not directly assessed fat and other macronutrient intake in a validated and reliable macronutrient self-selection paradigm. Pre- and post-menopausal female smokers were tested in our macronutrient self-selection paradigm (MSSP) while still smoking and then were enrolled in a two-week smoking cessation program. At one-month postcessation, the MSSP tests were repeated. Premenopausal women were tested during the late luteal phase of the menstrual cycle. Preliminary results obtained from both pre- and post-menopausal women suggest that females who quit smoking tend to increase their intake of high fat/high sugar foods. This effect cannot be generalized to all high fat/high carbohydrate foods, as neither group of women showed an increase in their intake of high fat/high complex carbohydrate foods postcessation. Foods that are high in both fat and sugar content are most likely to be associated with hyperphagia and weight gain and, therefore, may contribute to the weight gain that is often observed in women following smoking cessation. Supported by NIH grant AG18239 and the Bristol-Myers Squibb Foundation.

14. VASOPRESSIN AND SUGAR ADDICTION. Murphy, H. M.; Wideman, C. H. Neuroscience Program. John Carroll University, Cleveland, OH 44118 Although the term “addiction” is usually associated with drugs, the urge to eat sugar shares some of the physiological characteristics of drug dependence. Activity of the nucleus accumbens is key to the “high” sought by abusers of addictive substances and is also involved in regulating feeding. Intermittent, excessive sugar intake causes endogenous opioid dependence in rats and produces hormonal changes in the body that can enhance the seeking of sweets following a large increase of insulin in the blood produced as a reaction to a large increase in blood glucose. We have demonstrated that vasopressin (VP) influences sugar intake and metabolism. The purpose of this study was to determine if VP enhances or inhibits the development of sugar addiction. For four weeks, VP-containing (LE) and VP-deficient (DI) rats were provided with daily access to food for 12 hours. During weeks 2 and 4, animals had 12 hours access to 25% glucose in addition to food. Glucose and food intake were measured one-hour and twelve-hours after the presentation of these substances. Significance was found for both one-hour and twelve-hour glucose consumption for both strains of rats. There was an increase in glucose consumption in week 4 compared to week 2 and DI animals consumed more glucose than LE rats. During week 3, the rats were in a highly agitated state, with heads shaking and forepaws quivering with tremors. These

behaviors are characteristic of withdrawal. In week 4, all animals were found to exhibit bingeing behavior; however, DI animals consumed significantly more glucose and food than LE animals. It is concluded that both strains displayed classic symptoms of addiction, but these symptoms were exacerbated in DI rats.

15. SERUM TRIGLYCERIDES INDUCE LEPTIN RESISTANCE AT THE BLOOD-BRAIN BARRIER. Robinson, S.M.[1]; Banks, W.A.[1]; Nakaoke, R.[1,2]; Morley, J.E.[1] GRECC, Veterans Affairs Medical Center-St. Louis and Saint Louis University School of Medicine, Division of Geriatrics, Dept of Internal Medicine[1]; Dept of Pharmacology, Nagasaki University School of Medicine, Nagasaki, Japan[2] Leptin plays an important role in the regulation of feeding behavior. Leptin resistance has been proposed as a major factor in obesity and starvation. Resistance has three possible causes: a defect in the leptin transporter, a defect in the leptin receptor, or a blockade in downstream neuronal circuitry. Previous studies have shown that obese mice did not respond to an intravenous administration of leptin and transported leptin across the blood-brain barrier (BBB) poorly. They can, however, respond to leptin given centrally. This observation indicates the likelihood of a BBB transporter default. Leptin transport across the BBB is also impaired with starvation. Since serum triglyceride (TG) levels are elevated during both obesity and starvation, we postulated that TGs inhibit leptin transport across the BBB. Whole milk (of which the fat is 98% TGs) and three commercially available TGs (triolein, DPOG, DSOG) were tested to study the relation between TGs and leptin uptake. After iv injection, brain perfusion, and an *in vitro* brain monolayer model of the BBB, milk was found to be a potent inhibitor of transport. Triolein had a dose dependent effect on leptin transport and demonstrated a greater effect than the other commercial TGs. The administration of gemfibrozil, a drug used clinically to treat hypertriglyceridemia, resulted in a significant decrease in TG levels and an increase in leptin uptake when compared to control mice that did not receive the pharmacological intervention. Thus, TGs are likely an important mediator of the resistance to leptin at the BBB level in obesity and starvation.

16. CHRONIC IL-1β IN MICE AS A MODEL OF CACHEXIA. Joppa, M.A.; Wilson, J.; Behan, J.; Foster A.C.; Gogas, K.R.; Markison, S. Neurocrine Biosciences, Inc. San Diego, CA 92121. Cachexia, commonly associated with chronic diseases such as cancer and AIDS, is a wasting of body mass likely due to elevated metabolism and reduced feeding. Of the few murine cancers that do induce cachexia, the excessive growth of the tumor makes detection of body weight loss difficult and may ultimately impair mobility. The cytokine, IL-1β, has been described as one of the most potent mediators of cachexia. Thus, we delivered IL-1β via subcutaneous osmotic pump attempting to model the feeding and body composition changes that occur in cachexia. Doses of 0.3-3 mg/day were delivered for 7 days to mice housed in either standard cages or cages with running wheels. IL-1β infusion caused a dose-dependent reduction in body weight, which was most prominent during the first two days after pump implantation. Food intake was also dose-dependently reduced; mice given 0.3 mg/day recovered most quickly, while mice given 3 mg/day never recovered. Plasma IL-6 levels were highest 24 hours after the start of IL-1β infusion and remained elevated after 7 days of IL-1β. Body fat and lean mass were significantly reduced in mice given 3 ug/day of IL-1β while the lower doses caused loss of body fat only. Dark phase wheel running was significantly depressed on day 1 by both 0.3 and 1 mg/day (3 mg/day not tested) and the effect of 1 mg/day persisted through day 2. These findings suggest that chronic infusion of IL-1β may partially mimic the symptoms observed in cachexia, but mice eventually recover. While this model may prove useful to study effects on food intake, lean mass reduction was not affected until doses of IL-1β were extremely high.

Drugs and Behavior

17. MODULATION BY TYPE A AND TYPE B GABA RECEPTORS OF THE MOTOR RESPONSES PRODUCED BY D1-LIKE- AND/OR D2-LIKE DOPAMINERGIC AGONISTS IN THE RAT NUCLEUS ACCUMBENS. Chevallier, K.; Abraini J.H. Université de Caen, UMR CNRS 6185, centre CYCERON, Bd Becquerel BP5229, 14074 Caen cedex, FRANCE. The basal ganglia are a set of subcortical structures that regulates locomotion. The striatum is the major input structure of the basal ganglia. The nucleus accumbens, who is the ventral part of the striatum, receives major ascending dopaminergic mesolimbic projections from the ventral tegmental area and contains GABAergic interneurons. Many studies have shown that the output projection neurons of the nucleus accumbens expressed D1-like and D2-like dopamine receptors, both on GABA projection neurons of the striato-nigral pathway and on neurons of the striato-pallidal pathway, respectively. Although many functional studies have been performed on the role of accumbal dopaminergic neurotransmission in regulating locomotor activity, very few studies have been performed regarding the involvement of intrinsic neurotransmission, especially GABAergic interneurons, on the modulation of the locomotion induced by dopaminergic neurotransmission. The aim of our work was to study possible functional interactions between both D1-like and D2-like dopaminergic receptors and both GABAA and GABAB receptors in the rat nucleus accumbens. Bilateral intra-accumbal injections of either agonists or antagonists of GABAA or GABAB receptors were performed after administration of selective dopaminergic agonists in the nucleus accumbens. Immediately after drug treatments, locomotor activity was recorded for 90 minutes. Our study provides evidence for functional interactions between dopaminergic

neurotransmission mediated by both D1-like and D2-like receptors and intrinsic GABAergic neurotransmission mediated by both GABAA and GABAB receptors, those interactions depending of the type of receptors involved.

18. PHENOTYPICAL CHARACTERIZATION OF TRANSGENIC MICE OVEREXPRESSING HUMAN WILDTYPE ALPHA-SYNUCLEIN. Fleming, S.; Levine, M.; Masliah,E.; Chesselet, M-F. Departments of Neurology and Neurobiology, The Mental Retardation Research Center, UCLA, Los Angeles, CA, and Department of Pathology, UCSD, San Diego, CA The protein a-synuclein is thought to be involved in presynaptic neuronal function and is a major component of Lewy bodies, the pathological hallmark of Parkinson's disease. Transgenic mice expressing wild type human a-synuclein (ASO; Masliah et al. Science 287, 2000, 1265-9) exhibit anomalies in dopamine function, however their behavioral phenotype has not been characterized in detail. We have developed a battery of sensorimotor tests to examine the behavioral profile of these mice. Animals were repeatedly tested over the course of eight months for motor performance and coordination, spontaneous exploratory activity and sensory neglect. Shredding behavior was measured on separate groups of animals at varying ages. As early as two months of age, ASO animals displayed robust impairments in motor performance and coordination that persisted the length of the experiment. In addition, ASO animals showed reductions in spontaneous activity, sensory neglect, and shredding behavior. In a separate group of ASO and wildtype mice, the dopamine agonist apomorphine was administered and motor function was assessed. ASO mice displayed an enhanced response to low doses of apomorphine. These data demonstrate that ASO mice exhibit behavioral deficits compatible with a progressive dysfunction of the nigrostriatal dopaminergic pathway and provide the basis for phenotypic assessment in preclinical drug trials of mouse models of Parkinson's disease.

19. BLOCKADE OF NON-NMDA RECEPTORS PREVENTS NEUROTENSIN-INDUCED SENSITIZATION TO AMPHETAMINE. Rompré, P.-P.; Serio, M.; Bauco, P. Dept. of Psychiatry, University of Montreal, Montreal, Québec, H1N 3V2. Previous studies have shown that sensitization to amphetamine-induced locomotion is prevented by the neurotensin (NT) antagonist, SR-48692, and is initiated by repeated central activation of NT receptors (Rompré, 1997; Rompré & Perron, 2000). The present study was designed to determine whether activation of non-NMDA receptors is necessary for the development of amphetamine (AMPH) sensitization by repeated exposure to NT. During a first training period, locomotor activity (ambulatory, non-ambulatory and vertical movements) was measured in male Long-Evans rats on four occasions, every second day (day 1,3,5 and 7), for two hours after ICV injections of NBQX (0.1 and 1 μg/10 μl) or its vehicle followed by the NT analog, D-Tyr[11]NT (18 nmol/10 μl), or its vehicle. One week after, on day 14, locomotor responses to a single injection of AMPH (0.75 mg/kg, ip) were measured in all the rats. Results show that on the first testing day NBQX suppressed all parameters of locomotor activity in the first 30 min, and weakly attenuated the stimulant effect of NT but on non-ambulatory movements only. On day 14, amphetamine induced stronger ambulatory and non-ambulatory activity in NT pre-exposed animals than in controls (saline pre-exposed), a sensitization effect that was dose-orderly attenuated by NBQX. These results show that sensitization to amphetamine-induced locomotion by repeated NT is mediated, at least in part, by non-NMDA AMPA receptors, and that these receptors are unlikely to play a major role in the effect of NT on spontaneous locomotor responses. Supported by CIHR (Canada).

20. DO SOCIAL PEERS ACT AS CUES IN THE ACQUISITION OF CONDITIONED ETHANOL TOLERANCE? Martin, J.; Farmer-Dougan, V.; Siegel, S. Departments of Biology and Psychology Illinois State University, Normal, IL USA 61790. Department of Psychology, McMaster University, Hamilton, ON Canada. The hypothermic and motor effects of ethanol injections are mediated by predictive non-social environmental cues. This is the first study that examines the role of social peers as environmental cues. The present experiments propose to study the role of social peers as cues in ethanol tolerance acquisition using three manipulations. Experiment 1: Comparison of existing research design using non-social environmental cues and a design with rats as social cues in tolerance acquisition. Experiment 2: Social versus proximal environmental variables as cues for tolerance. Experiment 3: Discrimination of peers predicting ethanol and peers predicting saline inejctions.

21. DOPAMINE D1 AND D2 RECEPTOR FAMILIES CONTRIBUTE TO THE COCAINE-INDUCED DISRUPTION OF PREPULSE INHIBITION IN MICE. 1Doherty JM; 1Lehmann-Masten, V.; 2,3Low, MJ; 1Geyer, MA. 1Dept Psychiatry, UCSD, La Jolla, CA, 92093 USA; 2Vollum Institute, 3Dept Behavioral Neuroscience, OHSU, Portland, OR 97239 USA. Deficits in prepulse inhibition (PPI), an operational measure of sensorimotor gating, are characteristic of schizophrenia and related neuropsychiatric disorders. Clinical and animal studies demonstrate a contribution of the D1- and D2-families of dopamine (DA) receptor subtypes to the modulation of PPI. Receptor-gene knockout technology provides a powerful approach to study the role of individual receptors in vivo. Using genetically altered mice, we previously found that cocaine-induced disruption of PPI is attenuated in mice lacking the D1R and enhanced in mice lacking the D3R, demonstrating that D1R and D3R exert different influences on effects of cocaine on PPI in mice. Here, we used a combined pharmacological and genetic approach to further examine contributions of DA receptor subtypes to PPI. We tested PPI in D2R and D3R mutant mice treated with cocaine. Cocaine disrupted PPI in the WT and KO genotypes of both lines. SCH23390, a selective

DA D1-family antagonist, and raclopride, a selective DA D2-family antagonist, significantly blocked the cocaine-induced disruption of PPI in both D2WT and D3WT mice. SCH23390 blocked the disruption in PPI caused by cocaine in both D2KO and D3KO mice. Raclopride blocked the cocaine-induced disruption in PPI in D3KO mice but not in D2KO mice. These findings confirm that cocaine-induced disruption of PPI in mice is modulated by both DA D1 and D2 families of receptors. Uncovering neural mechanisms involved in PPI will further our understanding of substrates of sensorimotor gating and could lead to better therapeutics to treat complex cognitive disorders, such as schizophrenia.

22. EXERCISE POTENTIATES MORPHINE-INDUCED ANTINOCICEPTIVE TOLERANCE AND HYPERPHAGIA. Mathes, W.F.; Kanarek, R.B. Department of Psychology, Tufts University, Medford, MA 02155 USA Chronic running wheel activity attenuates the antinociceptive effects of opiate agonists. It is hypothesized that this effect is evidence for the development of cross-tolerance between endogenous opioid peptides released during exercise and the exogenous opiate being evaluated. Thus, repeated or chronic elevations in opioid peptide concentrations within the CNS may activate mechanisms similar to those activated following repeated morphine administration. If running wheel activity and repeated morphine administration act through similar mechanisms, it is expected that wheel running will alter other behaviors associated with repeated morphine administration, such as hyperphagia. To evaluate morphine-induced hyperphagia and antinociceptive tolerance in active and inactive animals, female rats were housed in activity wheels or standard cages for three weeks. Rats were then injected with morphine (10 mg/kg) daily for 10 days. Antinociceptive tolerance and hyperphagia were evaluated after 0,1,7and 10 days of morphine treatment and again after 9 days of drug abstinence. Active rats displayed tolerance and hyperphagia on day 1 of morphine treatment while the inactive rats did not show significant changes in food intake or antinociception until day 7. The results of this experiment demonstrate that running wheel activity potentiates the development of tolerance to morphine and augments the expression of sensitization to the hyperphagic effects of the drug. These results support the hypothesis that exercise leads to increased endogenous opioid activation which may contribute to the development of cross-tolerance and cross-sensitization with opiate drugs.

23. ENVIRONMENTAL FACTORS AND COCAINE PSEUDO-SENSITIZATION AND PSEUDO-TOLERANCE EFFECTS. Robert J. Carey, Research Dept., VA Medical Center and Dept. of Psychiatry, SUNY Upstate Medical University, Syracuse, NY Cocaine is a potent stimulant drug but its stimulant effects can be substantially modulated by environmental novelty versus familiarity. We experimentally manipulated familiarity to an environment by pre-exposures to a novel environment as a way to assess the impact of environmental familiarity versus novelty upon the locomotor activation induced by acute and chronic cocaine treatments. Following initiation of cocaine treatments in a novel environment, repeated treatments led to substantial decreases in the locomotor stimulant response induced by either 10.0 or 15.0 mg/kg cocaine. In contrast, either 1 or 10 pre-exposures resulted in a progressive increase in the locomotor stimulant response induced by repeated cocaine treatments. Whereas novelty amplifies, familiarity inhibits the locomotor stimulant effects induced by an acute cocaine treatment. With repeated cocaine treatments, however, both the novelty induced amplification and the familiarity induced inhibition subside resulting in pseudo-tolerance and pseudo-sensitization effects, respectively. While there is considerable interest in individual differences in reactivity to cocaine, the present findings point up the complementary importance of environmental context as a prominent factor in determining reactivity to cocaine.

24. GALANTAMINE/NICOTINE COMBINATION AS A NOVEL STRATEGY TO IMPROVE NICOTINIC THERAPEUTICS. Shytle RD; Townsend K; Sun N; Zeng J; Newman M; Sanberg PR; and Tan J. Center for Excellence in Aging and Brain Repair, Dept. of Neurosurgery; Child Development Center, Dept. of Psychiatry; Dept. of Pharmacology, and Neuroscience Program, University of South Florida College of Medicine, Tampa, FL. We recently reported that nicotine and acetylcholine (ACh) inhibited microglial activation (LPS-induced TNF-a release) at physiologically relevant concentrations. Our findings uncover a brain cholinergic pathway that regulates microglial activation through a7 nicotinic receptors (nAChR). Reducing neuroinflammation may be another mechanism for nicotine's reported neuroprotective effects. Using our in vitro model of microglial activation, we found that the combination of the potent allosteric nAChR agonist, galantamine (0.05 μM) and nicotine (1.0 μM) synergistically reduced microglial activation. In order to determine if galantamine+nicotine has a synergistic effect on behavioral endpoints, we treated adult male rats with nicotine (NIC; 0.2 mg/kg sc), Galantamine (GAL; 0.3-3.0 mg/kg sc), or their combination for eight days measuring locomotor activity on days 1 and 8. Following a one day washout, all rats received a test dose of NIC (0.2 mg/kg sc) to measure the sensitized locomotor stimulant response. NIC+GAL synergistically reduced locomotor activity on day one and this effect was still present on day 8. However, the sensitized locomotor stimulant response to NIC alone on day 10 was not altered in rats who had received subchronic NIC+GAL. Rats receiving GAL alone for 8 days did not show a sensitized locomotor response to nicotine. Because locomotor sensitization to nicotine involves neural substrates involved with nicotine dependence, these findings suggest that galantamine/nicotine cotherapy should have greater therapeutic efficacy (e.g. reducing neuroinflammation and/or improve cognitive function) than either drug alone without increasing the

abuse liability of nicotine. This work was supported in part by the Alzheimer's Association (JT) and a Florida Alzheimer's Center & Research Institute Award (DS and JT).

25. NICOTINE SENSITIZATION IN A RODENT MODEL OF PSYCHOSIS. Perna, M.K.; Smith, K.J.; Brown, R.W. Dept. of Psychology, East Tennessee State University, Johnson City, TN 37614 USA. Past data from this laboratory has demonstrated that neonatal quinpirole (dopamine D2 agonist) treatment produces long-term dopamine D2 receptor supersensitization. In this study, the offspring of four male-female breeder pairs were administered one daily i.p. injection of quinpirole (1 mg/kg) or saline from postnatal days 1-21 (P1-21) and raised to adulthood. Beginning on P65, rats were i.p. administered with either nicotine (0.5 mg/kg free base) or saline every second day and tested 10 min later in a locomotor arena. Groups were divided based on neonatal drug treatment (Quinpirole, Saline) and drug treatment in adulthood (Nicotine, Saline), and trials were aggregated into three blocks of three trials each. Analysis of horizontal line crossings after drug treatment in adulthood revealed a significant main effect of adulthood drug treatment $F(1,26)= 8.80$, $p<.001$; a significant interaction of Neonatal Treatment x Trial Block $F(2,26) = 3.14$, $p<.05$ and a significant interaction of Adulthood Treatment x Trial Block $F(2,26) = 30.6$, $p<.001$. By the last block of trials, the group receiving neonatal quinpirole treatment and nicotine in adulthood demonstrated significantly higher levels of activity than any other group, and the group receiving neonatal saline and adulthood nicotine treatment demonstrated increased activity relative to saline controls. An analysis of vertical rearing revealed a significant main effect of drug treatment in adulthood $F(1,26)=5.8$, $p<.02$ and a significant Neonatal drug treatment x Trial Block interaction $F(1,26)=3.6$, $p<.03$. Animals given nicotine demonstrated an overall decrease in vertical rearing, and animals given neonatal quinpirole treatment demonstrated a decrease in vertical rearing over trials, a possible manifestation of increased anxiety in these animals. An investigation is currently underway to analyze changes in receptor binding through autoradiography.

26. CHRONIC OLANZAPINE TREATMENT ELIMINATES COGNITIVE DEFICITS PRODUCED BY D2 RECEPTOR SUPERSENSITIZATION. Thacker, S. K.; Perna, M. K.; Smith, K. S.; Kostrzewa, R. M.; Brown, R. W. Department of Psychology, East Tennessee State University, Johnson City, TN 37614 USA. Olanzapine is an effective antipsychotic used to treat schizophrenia. We have developed a rodent model of psychosis through neonatal administration of quinpirole (D2 agonist) that produces long-term D2 receptor supersensitization. Rats were given quinpirole (1mg/kg) or saline treatment from P1-21. Beginning on P61, rats were administered olanzapine (2.5 mg/kg) or saline twice daily (i.p.) for 28 days. Beginning on P90, rats were tested on the place version of the Morris water task (MWT) for three consecutive days. A probe trial, with platform removed, was given at the end of training. The next day, animals began testing on the match-to-place version for four consecutive days and two daily trials were given with the platform moved to a new location each day. On the search time of the probe trial, a two-way ANOVA revealed significant main effects of neonatal drug treatment $F(1,36)=4.4$, $p<.04$; adult drug treatment $F(1,36)=3.5$, $p<.04$, and the Neonatal x Adulthood drug treatment interaction approached significance ($p=.06$). On target visits of the probe trial, the Neonatal x Adulthood drug treatment interaction was significant $F(1,36)=5.52$, $p<.02$. On both measures, neonatal quinpirole treatment produced cognitive deficits that were eliminated by adulthood olanzapine treatment. On the match-to-place version, the difference in latency to locate the platform between the two daily trials served as the dependent measure. The Neonatal x Adulthood drug treatment interaction was significant $F(1,36)=8.5$, $p<.006$. Similar to the place version, olanzapine treatment eliminated deficits produced by neonatal quinpirole treatment on this task. Analyses for neurotrophic factors and choline acetyltransferase in the hippocampus, frontal cortex, and parietal cortex are currently underway.

27. ACUTE ETICLOPRIDE TREATMENT ELIMINATES COGNITIVE DEFICITS PRODUCED BY NEONATAL QUINPIROLE TREATMENT. Thompson, K. N; Click, I. R.; Best, R. A. C.; Thacker, S. K.; Brown, R. W. Department of Psychology, East Tennessee State University, Johnson City, TN 37614 USA. This study was designed to investigate the effects of acute eticlopride (0.02 mg/kg, D2 antagonist) treatment, given immediately before training, in rats neonatally treated with quinpirole, which has been shown to produce long-term D2 receptor supersensitization. Rats were given quinpirole (1mg/kg) or saline treatment from P1-21. Beginning on P22, rats were administered eticlopride or saline (i.p.) fifteen mins before each of seven days of training. Rats were tested on the Morris water task (MWT). For the first three consecutive days, rats were tested on the place version of the MWT with a stationary platform. Animals were given 24 training trials followed by a probe trial, and swim patterns were analyzed with platform removed. The next day, animals began testing on the match-to-place version for four consecutive days and two daily trials were given with the platform moved to a new location each day. On both the search time and target visit measures of the probe trial, animals neonatally treated with quinpirole demonstrated a deficit, and eticlopride eliminated this deficit. Interestingly, animals neonatally treated with saline but given eticlopride before training also demonstrated a deficit on both measures. On the match-to-place version, the difference in latency to locate the platform between the two daily trials served as the dependent measure. Similar to the MWT place version, eticlopride treatment eliminated deficits produced by neonatal quinpirole treatment on this task, and eticlopride produced a deficit in saline controls. This study demonstrates that in a model of dopamine D2 supersensitivity, it appears that the increased sensitivity of the D2 receptor is important for cognitive function.

28. EFFECT OF 5HT2C/2A RECEPTOR AGONISTS AND ANTAGONISTS ON ICSS RESPONDING IN RATS. Martin, F.D.C.; Mac Sweeney, C.P.; Marston, H.M. Neurobiology Unit, Organon Laboratories, Newhouse ML15SH, Scotland. Intracranial self-stimulation (ICSS) has been shown to be a useful tool to study potential hedonic/anhedonic effect of drugs. However, the effects of 5HT2C/2A receptor ligands have not as yet been fully explored. The aim of the present study was to investigate the involvement of 5HT2C/2A receptors in ICSS responding. Sprague-Dawley rats were trained to respond for electrical stimulation in the lateral hypothalamus using the rate-frequency curve shift paradigm, and then tested with 5HT2C/2A ligands, following s.c. injection. The reward threshold (LOR) and the maximal number of responses (MAX) were determined using the Boltzman sigmoidal model. The mixed 5HT2C/2A agonist m-CPP significantly ($p<0.05$ vs baseline, one-way ANOVA followed by Tukey) decreased the MAX and increased the LOR at 1mg/kg. SB242084, a selective 5HT2C antagonist, had no effect alone (at 1mg/kg) but significantly attenuated the effect induced by m-CPP. MDL100,907, a selective 5HT2A antagonist, selectively increased LOR, with no change in MAX (at 0.1mg/kg), and potentiated the m-CPP deficit effects on MAX but not LOR. The mixed 5HT2A/2C agonist DOI (1mg/kg) provoked a significant decrease of MAX and increase of the LOR which was blocked by MDL100,907 but not by SB242084. This study showed that MDL100,907, m-CPP and DOI all increased the reward threshold for ICSS. Furthermore, the effects of m-CPP were selectively reversed by the 5HT2C receptor antagonist SB242084, whereas the effects of DOI were selectively reversed by the 5HT2A receptor antagonist MDL100,907. In conclusion, stimulation of either 5HT2A or 5HT2C receptor subtypes can modulate ICSS responding in rats. The effects of m-CPP were found to be mediated by 5HT2C receptors, and the effects of DOI were mediated by 5HT2A receptors.

29. REWARD-DEPENDENT INDUCTION OF FOS WITHIN LIMBIC BRAIN REGIONS. Marcangione, C.; Rompré, P-P. Centre de Recherche Fernand-Seguin, Dept. Psychiatry, University of Montreal, Montreal, H1N 3V2, Canada. Rats will readily self-administer electrical stimulation to the posterior mesencephalon (PM). We previously described a reward-relevant link between the PM and the ventral tegmental area (VTA) and showed that rewarding stimulation of the PM increases cell firing in some VTA dopamine cells and induces Fos within the VTA. The present experiment extended these findings by comparing Fos induction within limbic brain regions following rewarding and non-rewarding stimulation of the PM. Three groups of rats were implanted with an electrode and trained to lever-press for electrical stimulation. At the end of the training phase, rats were tested under the following conditions: Group 1 was allowed to self-stimulate for 1 hr, Group 2 was "yoked" to the rate of responding of Group 1 at non-rewarding stimulation parameters, while Group 3 was placed in the test cage, but received no stimulation. At the end of the final test, the rats were sacrificed, brains removed, and processed for Fos immunoreactivity. Both rewarding and non-rewarding stimulation induced Fos at the tip of the electrode, but greater labelling was seen in the self-stimulating rats. Only rewarding stimulation induced a prominent rostral-caudal distribution of Fos within the VTA and substantia nigra. Reward-dependant Fos expression was also observed in numerous limbic nuclei including the prefrontal cortex, nucleus accumbens, bed nucleus of the stria terminalis, lateral hypothalamus, subiculum, pontine nuclei, and the dorsal tegmental bundle. These findings allow us to better identify central brain regions that constitute an important component of the reward-relevant circuitry.

30. CROSS-SENSITIZATION BETWEEN BRAIN STIMULATION REWARD AND AMPHETAMINE-INDUCED LOCOMOTION. Boye, S.M. and Grant, R.J. Centre de Recherche Fernand-Seguin & Dept Psychiatry, University of Montreal, Montreal, Quebec, Canada. The rewarding effect of electrical brain stimulation is dopamine-dependent, as is the locomotor-activating effect of psychostimulant drugs. The present experiment examined the effect of prior experience with rewarding electrical brain stimulation (self-stimulation) on the locomotor response to amphetamine. Rats were first tested for their locomotor response to novelty (activity cage) and subsequently assigned to one of four groups in a way that distributed the responses to novelty in an unbiased way. The four groups were: 1) rats implanted with a stimulation electrode in the posterior mesencephalon and trained to self-stimulate (SS), 2) rats similarly implanted but never trained to self-stimulate (NO SS), 3) intact animals treated with amphetamine (AMPH), and 4) intact animals treated with saline (SAL). Rats in the SS group were trained to respond for stimulation parameters previously shown to trans-synaptically activate mesolimbic dopamine cells in a reward-specific manner. Throughout the two weeks of daily testing, the rewarding effectiveness of the stimulation was maintained constant across all SS rats. Rats in the NO SS group were handled daily but never tested. Twenty-four hours after the last test session, locomotor responses to amphetamine (0.5 mg/kg, ip; SS, NO SS and AMPH groups) and saline (SAL group) were measured during a one hour test. All three groups treated with amphetamine showed increased locomotor activity in comparison to the saline-treated group ($p<.01$). Additionally, rats in the SS group displayed higher locomotor activity in response to amphetamine than those in the AMPH group during the first half of the test (0-30 mins, $p<.01$) and higher activity than both NO SS and AMPH groups during the second half of the test (30-60 mins, both $p<.01$). These results suggest that prior exposure to rewarding electrical stimulation sensitizes the locomotor response to amphetamine.

31. THE ANABOLIC STEROID 17α-METHYLTESTOSTERONE MODULATES ANXIETY WHEN INFUSED INTO THE DORSOMEDIAL HYPOTHALAMUS ACCORDING TO SEX. Rivera, J.C.[1]; Morales, L.[1]; Vargas, N. M.[2] and Jorge, J. C.[2] Department of Biology[1], Río Piedras Campus and Department of Anatomy[2], Medical Sciences Campus. University of Puerto Rico, San Juan, P.R. 00936. The androgen 17α-methyltestosterone (17α-meT) is one of the most commonly abused anabolic androgenic steroids (AAS). We wanted to determine the behavioral effects of AAS after bilateral infusion of this androgen into the dorsomedial hypothalamus (DMH, coordinates DV 8.6, AP –2.8, ML ±0.5) in affective components of behavior according to sex. Control rats were infused with 0.9% saline whereas experimental animals were infused with 17α-meT, 1μM (0.5 μL/side) five minutes before each behavioral test. We found that central infusion of 17α-meT increased Social Interactions (SI) in females only ($p \leq 0.05$). Similarly, infusion of the $GABA_A$ receptor agonist muscimol, increased SI in females ($p \leq 0.05$). In addition, conflict-based anxiety was significantly modified in the Vogel Conflict Test (VCT). Specifically, we found that females infused with 17α-meT displayed a longer latency (s) to the first lick ($p \leq 0.05$) than their control counterparts accompanied by a tendency to received a greater number shocks. No significant differences were noted in VCT behavior among males. Changes in SI and VCT were not associated with changes in exploratory-based anxiety, locomotor activity, water intake, or anhedonia. We propose that modulation of $GABA_A$ receptors by AAS within the DMH can elicit changes in affective components of behavior. Support provided by NIH-BRIN award (P20RR16470) to JCR, PR-LSAMP-NSF (HRD0114586) to LM, and the MBRS-RISE Program at MSC-UPR (GM61838) to NMV. Study supported by NIH-COBRE (RR15565), NIH-BRIN (RR16470), and RCMI-MSC (RR03051) to JCJ.

32. EXPOSURE TO AN ANABOLIC STEROID PREVENTS THE ANXIOLYTIC EFFECTS OF ETHANOL. Rivera-Ramos,I.[1]; Rundle, V.[1]; Rojas, Y[2]; and Jorge, J.C [3] [1]Deparment of Biology, Rio Piedras Campus and [2]School of Medicine and [3]Deparment of Anatomy, Medical Sciences Campus, University of Puerto Rico, San Juan Puerto Rico, 00936 Clinical data suggests that anabolic androgenic steroid (AAS) abusers also ingest other drugs of abuse perhaps in an attempt to ameliorate the disruptive effects of AAS exposure in affective components of behavior. We employed adult C57Bl/6 male mice which were exposed to the AAS 17a- methyltestosterone (1μM) via a subcutaneous osmotic pump (0.55μl/hr for 16 days; Azlet Co., CA). Controls received vehicle implants (0.9M NaCl + 30% cyclodextrine). Half of the animals for each group received either an ethanol (EtOH) injection (i.p.; 2mg/kg) or a saline injection on days 14 and 15. Five min after the injection, animals were tested in an automated elevated plus maze (EPM; day 14) or automated activity chambers (day 15) (AccuScan Instrument, Ohio). Animals were tested for ethanol consumption on day 16. We found that non-exposed AAS animals and made more entries into the open arms ($p < 0.05$) of the EPM upon EtOH exposure than AAS-exposed animals. These changes were not associated with sedation as assessed with locomotor behaviors. We did not detect significant changes in EtOH consumption among groups. These data indicate that prior exposure to AAS prevents the anxiolytic effects of EtOH. Support provided by the BRIN Undergraduate Research Program (RR16470) to IRR, and the MBRS-RISE Program at MSC-UPR (GM61838) to VRG and the Howard Hughes Undergraduate Research Program to YR. Study funded by NIH-COBRE (RR15565), a Young Investigator Award (NIH-BRIN, RR16470), and the RCMI Program at MSC-UPR (G12RR03051) to JCJ.

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33. ANABOLIC STEROID EFFECTS ON GABA IMMUNOREACTIVITY IN DISCRETE BRAIN NUCLEI. V Rundle-González[1], I Rivera-Ramos[1], J Estrada-Barreto[2], JC Jorge[3] [1]Department of Biology-Río Piedras Campus, [3]Department of Anatomy-Medical Sciences Campus, University of Puerto Rico – San Juan, PR [2]Department of Sciences, Mathematics, and Technology, Universidad del Este – Carolina, PR Anabolic androgenic steroids (AAS) are derivatives of testosterone synthesized to treat a variety of medical conditions. Lately, its misuse has led humans from different ages to suffer from a diverse spectrum of side effects, in which we may find the alteration of endocrine functions and affect. In this study, we investigated the effects of AAS on γ-aminobutyric acid immunoreactivity (GABA-IR) in discrete brain regions of C57Bl/6 mice to evaluate the basic neural mechanisms underlying these alterations. Intact females received the AAS 17α-methyltestosterone (17α-meT; 7.5 mg/kg) or saline for a two-week period through an osmotic pump placed subcutaneously. Brain sections (14 μm) were obtained through the levels of the nucleus accumbens (NAc), the medial preoptic area (mPOA), the basolateral amygdala (AMY-bla), the ventromedial nucleus of the hypothalamus (VMN), an the ventral tegmental area (VTA). Sections were stained for GABA by immunohistochemistry methods. We observed an increase in GABA-IR cells in the NAc core and shell, and the VMN ($p \leq 0.05$) after AAS exposure. These changes were accompanied by a decrease in GABA-IR cells in the AMY-bla and the mPOA ($p \leq 0.05$). No changes in GABA-IR were observed in the VTA. Our data shows that exposure to 17α-meT produces region-specific effects in GABA-IR cells, suggesting that the GABAergic system may mediate some of the behavioral and the endocrine effects that are induced upon androgen exposure. Support provided by the MBRS-RISE Program at MSC-UPR (GM61838) to VRG, and the

BRIN Undergraduate Research Program (RR16470) to IRR. Study funded by NIH-COBRE (RR15565), a Young Investigator Award (NIH-BRIN, RR16470), and the RCMI Program at MSC-UPR (G12RR03051) to JCJ.

34. FUNCTIONAL INTERACTIONS BETWEEN DOPAMINERGIC RECEPTORS AND GROUP II METABOTROPIC GLUTAMATERGIC RECEPTORS IN THE RAT NUCLEUS ACCUMBENS. David, H.N.; Abraini, J.H. UMR CNRS 6185, CYCERON, University of Caen, BP 5229, Caen cedex, France. There is strong evidence for the existence of functional interactions between metabotropic glutamatergic (mGlu) receptors and dopaminergic neurotransmission in the rat nucleus accumbens. In the present study, we investigated the interactions between group II mGlu receptors and D1-like- and D2-like receptors, in the rat nucleus accumbens, on locomotor activity and the role of group II mGlu receptors on accumbal dopamine release. Administration of the selective group II mGlu receptor agonist APDC, which had no effect when injected alone, potentiated the locomotor response produced by the selective D1-like receptor agonist SKF 38393 but had no effect on those induced by the selective D2-like receptor agonist quinpirole – a compound believed to act only at D2-like presynaptic receptors when injected alone- or a co-administration of SKF 38393 + quinpirole – a pharmacological condition thought to stimulate both D1-like receptors and presynaptic and postsynaptic D2-like receptors. In contrast, the selective group II mGlu receptor antagonist LY 341495, which induced an increase in basal locomotor activity, showed no effect on the SKF 38393-induced locomotor response, but abolished that produced by quinpirole or SKF 38393 + quinpirole. The present findings demonstrate that stimulation of group II mGlu receptors has a cooperative and potentiating action on the locomotor response induced by D1-like receptor activation, whereas blockade of group II mGlu receptors has an antagonist action on the locomotor responses induced by activation of D2-like receptors. Finally, neurochemical results also showed that group II mGlu receptors modulate accumbal dopamine release.

35. OREXIN-B EXCITES THE NEURONS IN THE PARAVENTRICULAR NUCLEUS OF THE THALAMUS OF RATS. Sasaki, K.; Ishibashi, M.; Takano, S.; Yanagida, H.; Takatsuna, M.; Nakajima, K.; Oomura, Y.[1] Div. of Bio-Information Eng., Toyama Univ., Toyama, Japan; [1]Dept. of Physiol., Kyushu Univ., Fukuoka, Japan. The paraventricular nucleus of the thalamus (PVT), a periventricular constituent of the thalamic midline, is related to a basal ganglia-thalamocortical system implicated in the cognitive, emotional and visceral concomitants of behavior. Orexin-containing neurons in the lateral hypothalamus strongly project to the PVT. In the present study, we examined effects of orexin-B on the neuronal activity of the PVT in rats using brain slice preparations. Extracellular recordings showed that bath application of orexin-B under normal Ringer solution at doses of 10^{-8}, 10^{-7} and 10^{-6} M excited the activity in 5% (n=20), 54% (n=24) and 78% (n=9) of the PVT neurons recorded, respectively. None of the PVT neurons responded with inhibition to orexin-B. PVT neurons facilitated by 10-7 M orexin-B under normal Ringer solution were also facilitated by orexin-B with the same dose under low-Ca^{2+}, high-Mg^{2+} Ringer solution. Whole cell patch clamp recordings showed that orexin-B depolarized PVT neurons with an increase of membrane resistance. When the reversal potential of the depolarization was investigated, it was almost equal to the equilibrium potential of potassium ion. In addition, the increase of the extracellular concentration of potassium ion to 12 mM abolished the depolarization induced by orexin-B. These results suggest that orexin-B excites the most of PVT neurons via the closing of potassium channels, and that brain functions related to the PVT may be modulated by orexin-B.

36. THE EFFECTS OF ACUTE PCP ADMINISTRATION ON THE P300 EVENT RELATED POTENTIAL IN RATS. Franck, L.; Klipec, W.D.; Schneider, B.; Maffin. L Department of Psychology, Drake University, Des Moines, IA, 50311 USA. Research in our laboratory has demonstrated a rat model that produces a robust P300 ERP, the amplitude of which is an incremental function of the proximity of conditioned reinforcers to primary the reinforcer in behavioral chains. This rat P300 model has the potential for investigating the biochemical bases of the P300 ERP through pharmacological manipulations. McCarley et. al., (1993) reported decreased amplitude and bilateral asymmetry in the P300 in male human schizophrenics. Animal models of schizophrenia have been developed with PCP induced psychosis emerging as the most widely used model. Accordingly, the present experiment investigated the effects of acute PCP administration on the P300 ERP in rats, pursuant to investigating a chronic administration model of PCP induced schizophrenia. Rats were trained in a paradigm where lever insertion was cued by a 2.5 KHz tone with a non-target white noise burst presented (8:1 non-target to target ratio). Responding on the lever produced a food reinforcer on a VR-6 schedule with a cue light, followed by the click of the pellet dispenser signaling delivery of the food pellet. A descending then ascending series of i.p. PCP (4, 2, 1, 2, and 3mg/kg) was interspersed with no injection and saline control days. Compared to saline control days, we found a dose dependent decrease in the latency of the P300 ERP to the click of the food magazine (secondary reinforcer), with no significant effect on P300 ERP amplitude. These rats are currently being treated with chronic 5.0 mg/kg doses of PCP during and after which their P300 ERPs will be compared to pre-PCP baseline recordings.

37. ANTICONVULSANT POTENTIAL OF AMILORIDE IN PENTYLENETETRAZOLE-INDUCED KINDLING IN MICE. Ali, A.; Vohora, D.; Ahmad, F.J.; Pillai, K.K. Dept. of Pharmacology, Faculty of Pharmacy, Jamia Hamdard, New Delhi-110062, India. This study was performed to investigate whether or not amiloride can

protect against seizure development of pentylenetetraxole (PTZ)-induced kindling in mice. Kindling was induced by every other day treatment with PTZ (25 mg/kg i.p.) for five weeks. Challenge experiments were carried out after 15 or 30 days of last treatment with PTZ. Administration of amiloride (0.65 and 1.3 mg/kg p.o.), a sodium-hydrogen exchanger inhibitor significantly prolonged the onset of kindling and inhibited the seizure severity in a dose-dependent manner. Amiloride pretreatment also significantly reduced the incidence of seizures in animals treated with PTZ. Moreover amiloride exhibited protection against PTZ-induced seizures even after 15 or 30 days of last treatment. Therefore, the results indicate that amiloride plays a certain protective role on seizure development of PTZ-induced kindling in mice, and that its protective roles are probably mediated by sodium-hydrogen exchangers.

Stress and Depression

38. STRAIN AND SEX-SPECIFIC EFFECTS OF UNPREDICTABLE CHRONIC MILD STRESS ON DEPRESSIVE BEHAVIOR IN MICE. Yann S. Mineur and Wim E. Crusio. BNRI, UMass Medical School, Worcester, MA 01604, USA. Unpredictable chronic mild stress (UCMS) is one of the most popular and widely used animal models of depression, although it remains somewhat controversial. This is despite the fact that this model tries to mimic depression in a comprehensive form and presents robust pharmacological validation as well as excellent face validity. However, results are often said to be difficult to reproduce, sometimes even within laboratories. In a set of experiments, we subjected males and females of three different strains to UCMS and measured the state of their fur and body weight, and their performances in the tail suspension test and the forced-swim test. The latter two measures are popular assays of anti-depressive action (often incorrectly termed "models of depression"). The results revealed multiple interactions between treatment, sex, and strain and, furthermore, differed considerably between different tests. In other words, the effects of UCMS depend on the strain and sex of the subject, as well as on the way in which "depression" is assayed. It is generally agreed that complex interactions of genetic and environmental factors underlie major depression in humans. Our results suggest that the UCMS model mimics this situation. In addition, the tail suspension and forced-swim tests are often presented as alternatives, which basically test the *same* type of behaviors. However, our results show that identical treatments in the same animals can lead to quantitatively and qualitatively different effects in these tests. In conclusion: 1/ UCMS applied to multiple inbred strains models depressive-like behavior in a manner very reminiscent of the situation in humans, with some genotypes more susceptible to become depressed than others. 2/ Tests of depressive-like behavior, despite apparent similarities, do not measure the same underlying processes.

39. EXPOSURE TO CHRONIC UNPREDICTABLE STRESS REDUCES ESCAPE BEHAVIOR IN THE RAT. Gouirand, A.G.; Nilges, M.R.; Matuszewich, L. Dept of Psychology. The Northern Illinois University, Dekalb Il, 60115. An individual exposed to long-term stress may become vulnerable to depressive illness, which could include behavioral changes in motivation, emotion and cognition. Rodents are often exposed to stress regimens in the attempt to induce behavioral dysfunctions comparable to those seen in humans with depression. In the present investigation, rats were exposed to a chronic unpredictable stress paradigm (CUS) and then observed for behavioral changes in a modified forced swim test (FST). Specifically, the FST focuses on an animal's level of emotionality and motivation by assessing escape and immobility behaviors during an interval of swimming (Porsolt, Le Pichon, & Jalfre, 1977). The current study hypothesized that rats exposed to CUS would show an increase in immobility and decrease in escape behaviors, suggesting a decrease in natural motivation and increase in emotionality. Male rats were divided into 2 groups, stressed or non-stressed controls. The stressed rats were exposed to 10 days of randomly assigned stressors, including restraint stress, food and water deprivation, cage rotation, and light cycle changes (Matuszewich and Yamamoto, 2003). On the 11th day, all rats were individually placed into a container (20" tall) filled to 17" with water for 10 minutes and their behaviors recorded. Rats exposed to CUS showed a significant decrease in total time exhibiting escape behaviors ($t(27)=3.8, p<.01$), as well as for each 5 minute interval ($F(1,27)=15.1, p<.01$). There was no significant change in the latency to the immobility posture ($t(27)=.4$,n.s.) or the total time exhibiting immobility ($t(27)=.2$,n.s.). These findings suggest that CUS can influence some behavioral parameters of the FST and may be an appropriate animal model of depression when targeting decreases in natural motivational behaviors.

40. DOSE-DEPENDENT EFFECT OF REPEATED CORTICOSTERONE ON DEPRESSION-LIKE BEHAVIOR IN MALE RATS. Johnson, S.A.; Stamp, J.A.; Kalynchuk, L.E. Dept. of Psychology and Neuroscience Institute, Dalhousie University, Halifax, NS B3H 4J1 Canada. Repeated exposure to stress alters hypothalamic-pituitary-adrenal (HPA) axis function, and is a risk factor for the development of affective disorders in humans. However, little is known about the precise relation between stress and the pathogenesis of depression because most currently used animal models of repeated stress produce inconsistent behavioral changes. Recent data from our laboratory have shown that repeated high dose injections of corticosterone (CORT) increase depression-like behavior on a modified version of the Porsolt forced swim test. The present study served to replicate these findings and to determine the extent to which these effects were dependent on the dose of CORT. Separate groups of rats received

either a low dose injection of CORT (10mg/kg), an intermediate dose injection of CORT (20mg/kg), a high dose injection of CORT (40mg/kg), or a vehicle injection every day for 21 consecutive days. Forced-swim testing was conducted on day 22 to assess depression-like behavior. CORT affected several forced-swim behaviors in a dose-dependent manner. Specifically, the latency to immobility and time spent struggling decreased with increasing doses of CORT, whereas time spent immobile increased with increasing doses of CORT. Furthermore, higher doses of CORT had greater effects on body weight. These results confirm that repeated CORT injections produce reliable and robust increases in depression-like behavior in rodents, and show for the first time that these effects are dose-dependent. This suggests that the 21-day CORT injection paradigm may be a particularly useful animal model for studying the relation between repeated stress and depression.

41. EFFECTS OF DIFFERENT KINDS OF PARADOXAL SLEEP DEPRIVATION ON AGGRESSIVE BEHAVIOR INDUCED BY APOMORPHIN IN RATS. Motta, S.C.[1]; Calzavara, M. B.[2]; Frussa Filho, R.[2]; Leite, J. R.[1] [1]Departamento de Psicobiologia. [2]Departamento de Farmacologia. Universidade Federal de São Paulo. São Paulo. Brazil. Aggressive Behavior is widely expressed in almost every known animal species. Wistar rats paradoxal sleep deprived treated with apomorphin present this kind of behavior. Sleep deprivation can be made by two methods: single platform (more stressful) and multiples platforms (less stressful). This study objected the comparison of the effectiveness of this two methods acutely inducing aggression with different apomorphin doses. It was observed a diminished expression of the aggressive behavior with the drug's highest dose in the less stressful method compared with the others situations. This suggest that different kind of paradoxical sleep deprivation could shows specifics effects over the predominance of the expression of different behaviors, aggressive or stereotyped, on animals treated with apomorphin.

42. SOCIAL BEHAVIOR IN A RESIDENT-INTRUDER TEST PREDICTS INDIVIDUAL VULNERABILITY TO STRESS-INDUCED ANHEDONIA IN C57BL/6N MICE. Strekalova T; Frynta D; Berger S; Henn F; Bartsch D. Dept. of Molecular biology, Central Institute of Mental Health J5 68159 Mannheim, Germany. In order to model anhedonia, a core symptom of human depression, we subjected male C57BL/6 mice to a 4-week long chronic stress procedure, comprising of a rat exposure and restrained stress. This procedure resulted in a strong decrease of sucrose preference, a measure of anhedonia in rodents. Interestingly, not all animals developed anhedonia in a course of chronic stress. Animals with no decrease in sucrose preference were regarded as resistant to stress-induced anhedonia and were used as an internal control for the effects of chronic stress. Vulnerability to stress-induced anhedonia was reflected by social behavior in a resident-intruder test, evaluated before the beginning of stress procedure. All mice with submissive social behavior showed a strong decrease in sucrose preference and were assigned to anhedonic group. In contrast, most of the animals with aggressive behavior did not develop anhedonia. Those mice with aggressive social behavior, which developed hedonic deficit in a course of stress, were found to have significantly lower scores of aggressivity (measured by latency of attack and number of attacks), as compared to aggressive individuals from resistant to anhedonia group. Behavioral analysis performed after terminating the stress procedure demonstrated that anhedonia is associated with key analogues of depressive symptoms which cannot be seen in stressed animals without hedonic deficit, such as increased floating in forced swimming, decreased exploration of novelty and increased immobilization time in tail suspension test. Thus, individual vulnerability to development of anhedonia and of depressive-like behaviors in a course of chronic stress can be predicted by type of social behavior. This model can be applied in studies of epigenetic aspects of depression

43. DOES NEONATAL STRESS IMPACT CONTROL MOUSE BEHAVIOR IN A SPLIT LITTER DESIGN? Beard, N.; Singletary, L.; Hohmann, C.F. Department of Biology Morgan State University, Baltimore, MD 21251, USA. Environmental triggers are evident in the etiology of many mental health disorders; thus, a better understanding of the relationship between early stress and later onset of behavioral alterations is needed. Using a split litter design, we previously have reported that neonatal temperature/separation stress leads to substantial morphological and behavioral changes by adulthood in Balb/CByJ mice. Here we test if neonatally stressed and litter mate control mice perform comparable to age matched mice in an open field object recognition [OFOR] task. Between postnatal days (PND) 1 and 7, 6 male mice were exposed on alternating days to 30 minutes of cold (4C) or hot (37C) stress and 6 male litter mates remained with their dams. These mice, plus a cohort of 5 age matched male Balb/CByJ control mice, were tested on the OFOR task at 3 month postnatal. Behavioral performances were recorded on video-tape and analyzed using the Observer Video Pro II 4.0 system (Noldus). Data analysis was performed using factorial ANOVAs (StatView). Normal age matched mice significantly differed from the stressed and unstressed litter mate cohort in regards to overall object exploration as well as novelty response but they did not significantly differ in general activity levels. This confirms previous observations that neonatal stress alters exploratory behavior but also suggests that litter-mate controls to the stressed mice are not behaviorally normal, perhaps due to maternal care differences. Supported by: SO6-GM051971 and 1G12RR17581. forebrain bundle of Balb/CByJ mice, at birth, result in transient 5-HT depletions of the developing cortex and increased widths of cortical layers by adulthood. Moreover, these mice displayed impaired retention of passive avoidance behavior and improved performance on a non-matched-to-sample odor discrimination task. The present talk will focus on the

development of behavioral tasks to ascertain if these neonatally 5-HT depleted mice show behaviors interpretable as autistic and we will examine what should be regarded as mouse appropriate behavior for "autism". Moreover, we will discuss strategies to correlate structural alterations in the brain of these mice with behavioral measures and their usefulness in illuminating the neurobiological substrate of autism. Supported by NIHNCRR-1G12RR17581, NAAR and U54 MH066417-01A1.

44. MATERNAL EXPERIENCE MODIFIES RESPONSIVENESS TO NOVEL STIMULI IN YOUNG AND SENESCENT LONG-EVANS RATS. Torrey [1], N.; Love[1], G., McNamara[2], I.; Brown[3], K.; Glasper[4], E.; DeVries[4], A.C.; Kinsley[2], C.H., & Lambert[1], K.G. [1]Dept. of Psychology, Randolph-Macon College, Ashland, VA 23005; [2]Dept. of Psychology, University of Richmond, VA 23173; [3]Dept of Psychology, Virginia Union University, Richmond, VA 23220; [4]Dept. of Psychology, Ohio State University, Columbus, OH 43210 Maternal experience alters behavior and neurobiology to facilitate survival of the offspring. For example, we have found that motherhood facilitates spatial learning in a foraging task (Kinsley et al., 1999; Gatewood et al., 2003) and mitigates stress responsivity in the elevated plus maze (Love et al., 2003) across the rat's lifespan. Accordingly, the purpose of the present study was to assess the effect of maternal experience on responsiveness to novel stimuli in young adult and senescent Long-Evans rats. In Exp. 1, appx. 1.5 mos following pup exposure, nulliparous, primiparous, and multiparous rats (n=8 each group; 5 mos of age) were tested in an open field arena with novel stimuli (see Cavigelli et al., 2004). In Exp 2, 22-month old rats (n=7 each group; animals were part of a lifespan cognitive/emotional behavior study) were subjected to the same novelty test (18 mos following pup exposure). In both studies, blood for corticosterone analysis was collected from all animals following a two-minute swim and five-minute recovery. In Exp. 1, young adult multiparous rats crossed the center of the open-field significantly more times than the other groups and primiparous and multiparous rats approached novel stimuli faster than virgins (nonsignifant trend). Focusing on the senescent rats, multiparous rats exhibited more exploratory behavior than nulliparous counterparts; specifically, crossed more center lines, contacted more novel stimuli, and spent more time in contact with novel stimuli. There were no statistical differences in corticosterone levels in either the young or senescent animals; however senescent primiparous rats had 14% lower values than nulliparous rats. The results suggest that maternal experience facilitated exploratory behavior in the open field/novel stimuli arena.

45. EFFECT OF MATERNAL CARE AND STAGE OF ESTRUS ON NEUROENDOCRINE RESPONSE TO ACUATE STRESS. Cameron, N.M.; Sharma, S.; Meaney, M.J. Douglas Hospital Research Center, Verdun, Qc, Canada. Early-life experiences are known to cause changes in the HPA axis, and to regulate emotional and stress reactivity. As adults, rats that received low levels of maternal licking/grooming (LG) show greater HPA axis activity in response to stress compared to offspring of high LG mothers. High and low LG mothers and their female offspring display alterations in the expression of estrogen-receptor (ER) alpha, suggesting they may also differ in neuroendocrine function. Estrus and diestrus female offspring from low and high LG mothers experienced restraint stress for 30 min or no stress (control). Blood samples were collected at 30 or 90 min after stress. Control animals were sample from their home cage. Plasma estradiol (E2), progesterone (P), corticosterone (B) and corticosteroid-binding globulin (CBG) levels were analysed using radioimmunoassay. High LG females in both estrus and diestrus groups showed lower CBG level 30 min after stress than control or 90 min post-stress groups. This effect was not seen in the Low LG animals. 30 min after stress, B level was higher than controls in all the groups. Estrus Low LG females showed elevated B level at both 30 and 90 min after stress. High LG females in the estrus group showed higher P level 30 and 90 min after stress than the control group; no effect of stress was seen in diestrus animals. In contrast, diestrus Low LG females showed higher level of P in the 30 min group compared with the control and the 90 min groups, with no effect in the estrus animals. E2 levels were not affected by variations in maternal care, stage of estrus or by stress. Variations in maternal care may regulate the response to stress of the female offspring by altering B, CBG and P level.

46. MATERNAL SEPARATION INCREASES STRESS-INDUCED FOS EXPRESSION IN THE PVN OF BORDERLINE HYPERTENSIVE RATS. B.J. Sanders and A. Anticevic. Department of Psychology and the Neuroscience Program, Drake University, Des Moines, IA 50311 USA. During the preweaning period rodents are vulnerable to a variety of exogenous influences which can affect future development. Brief separation from the nest, sometimes called handling, and longer periods (e.g. 3 hours) of maternal separation are two common procedures used to study how early experience shapes an organism's developmental trajectory. Our lab uses an animal model of enhanced cardiovascular and behavioral reactivity to exploit this vulnerability to early adverse experiences. In this study, we examined whether 3 hours of daily maternal separation (MS) alters cardiovascular, behavioral and neurobiological responses to stress in adulthood. Borderline hypertensive (BHR) and normotensive Wistar-Kyoto (WKY) pups were isolated individually from the dam and other littermates on postnatal days 1-14. Mean arterial pressure (MAP) during rest and restraint stress, exploratory behavior in the open field, and restraint-stress induced neuronal activation in the paraventricular nucleus (PVN) and bed nucleus of the stria terminalis (BST) as assessed by c-Fos expression were measured in adult male offspring of both strains. Analysis of the MAP data revealed that BHR subjects had significantly higher resting and stress MAP compared to WKY, although separation had no effect

on either strain. When placed in the open field for 30 minutes, BHR-MS showed more exploratory behavior both in total and in the center of the arena compared to all other groups. Finally, 30 minutes of restraint stress produced a significant increase in Fos immunoreactive cells in the PVN of BHR-MS compared to non-separated BHR (57.7±8.3 vs 23.5±4.1). These results suggest that maternal separation has an enduring effect on behavioral and neurobiological responses to novel and stressful situations in adult BHR. Supported by NIH-HL073894.

47. EXTINCTION-INDUCED DESPAIR IN THE WATER MAZE: PROMISE OF A CONCEPTUAL AND EMPIRICAL MODEL OF HUMAN DEPRESSION Schulz, D.; Topic, B.; De Souza Silva, M.A.; Huston, J.P. Institute of Physiological Psychology, University of Düsseldorf, Düsseldorf, Germany Extinction of escape behavior in the water maze due to the removal of the platform, was hypothesized to induce a negative state, including the development of immobility, which is held to reflect a state of "despair" when measured in the forced swimming test. 27 aged and 8 adult animals (26 and 3 months old, respectively) were tested in the water maze during 9 days with a platform hidden, followed by 7 days of extinction trials with the platform absent. As expected, in both age groups the levels of immobility increased over the extinction trials, as did the number of animals that displayed immobility. Additionally, the aged showed higher levels of immobility than the adults, which was partially explained by the lower escape performance in this group. We also analyzed the amount of immobility shown separately for four different time intervals of each extinction trial, and found that most immobility occurred during the first min of the two min trials in both age groups. Immobility scores were then correlated with post-mortem neurotransmitter contents in the hippocampus and ventral striatum. In the ventral striatum, levels of immobility were correlated with levels of acetylcholine, dopamine and the metabolite DOPAC in the aged, and with norepinephrine in the adults. The data support the hypothesis that multiple extinction trials in the water maze result in immobility that may indicate "behavioral despair", and that striatal neurotransmitter systems correlate with the degree of its expression. The concept of extinction-induced despair is held to provide the promise of a conceptual and empirical model of human depression that is the consequence of loss of reinforcers.

48. MODELING DIFFERENTIAL RESPONSES TO ESTROGEN IN TWO RAT STRAINS. Koss, W.A.; Einat, H.*; Iqbal, S.A.; Manji, H.K.*; Rubinow, D.R. BEB & LMP*, NIMH, NIH, DHHS. Clinical studies from our laboratory have previously found that women who present symptoms of premenstrual syndrome (PMS) have an abnormal response to normal hormonal changes when compared to normal controls. These clinical findings suggest a differential sensitivity to reproductive hormones. To further investigate the underlying mechanisms of these variations we have attempted to model them in rats by exploring possible dissimilarities in response to estrogen in the forced swim test (FST) between two rat strains, Long evans and Wistar. In two different experiments, 2 groups of OVX rats were treated with estradiol (2.5ug/rat x 3 days) and 1 group with vehicle. One of the estrogen treated groups received estradiol 48, 24, and 2 hours before testing, whereas the other group was treated for 3 days and then withdrawn from estrogen for 3 days before testing. The two strains demonstrated differential responses to estrogen. Estrogen induced an antidepressive-like effect in Long Evans rats but not in Wistar rats. Conversely, withdrawal from estrogen resulted in a depressive-like state in the Wistar rats but not in the Long Evans rats. In conclusion, this dissociation across strains may serve as a model, representing differential sensitivities to changes of estrogen in women. Such a model will allow further investigations into the molecular and biochemical mechanisms of PMS.

49. SUBMISSIVE BEHAVIOR MEASURED IN RATS COMPETING FOR FOOD AS A MODEL OF DEPRESSION: STUDY WITH AUTOMATIC SCORING. Crooke, J., Pinhasov, A., Rosenthal, D., Brenneman, D.E., and Malatynska E. Johnson & Johnson Pharmaceutical Research & Development, L.L.C, Spring House, PA 19477, U.S.A. Previous studies have demonstrated that treatment with known antidepressants attenuated submissive behavior in rodents competing for food (Malatynska et al., 2002, Crooke et al., 2003). Pairs of rats compete during a daily 5-min trial period for a limited amount of food. About 25% of the rats develop a dominant-submissive relationship that can be measured as the amount of time spent on the feeder relative to that of the paired dominant animal. In the present study, scoring of the time spent by rats in the feeder area was done by multiple subject video-tracking system (PanLab/San Diego Instruments, San Diego, CA). This method allowed observation of four pairs of animals simultaneously. Using this automated method, validation studies with known antidepressants were conducted. Treatment of the submissive rats for five weeks with imipramine (20 mg/kg) or maprotyline (10 and 20 mg/kg) or fluoxetine (5 and 10 mg/kg) significantly reduced submissive behavior. Dose-related effects were observed for all antidepressant drugs studied. The onset of the antidepressant effect was delayed and the delay inversely correlated with the dose of antidepressant drug. A non-antidepressant drug, delta opioid receptor antagonist, naltrindole (10 mg/kg), was ineffective. Studies with imipramine and fluoxetine confirm our previous results with manual scoring. With this automated procedure, this model gains further utility by the increased capacity for testing a greater number of animals and the reduction in the variability of the paradigm. Screening of antidepressant drug compounds with the submissive model becomes more feasible with this methodology.

50. GAMMA SYNUCLEIN MRNA LEVELS DIFFER IN THE CORTEX OF SUBMISSIVE AND DOMINANT RATS SELECTED IN THE COMPETITION TEST. Pinhasov, A., Ilyin, S.E., Crooke, J., Amato, F.A., Vaidya, A.H., Rosenthal, D., Brenneman, D.E. and Malatynska, E. Johnson & Johnson Pharmaceutical Research & Development L.L.C., Spring House, PA 19477, U.S.A. Dominance and submissiveness has been defined in a competition test and measured as the relative success of two food-restricted rats to gain access to a feeder. Previous studies have shown that dominant behavior can serve as a model of mania and submissive behavior as a model of depression [Malatynska, et al., 2002a; Malatynska, et al., 2002b]. Three groups of rats have been defined under such conditions; dominant, submissive and neutral. The mRNA isolated from different regions of the rat cortex has been screened with cDNA microarray library of genes. Gamma-synuclein was identified as one of the genes differentially expressed between dominant and submissive rat groups. Using TaqMan RT-PCR technology, expression of alpha, beta and gamma synucleins was analyzed in four regions of dominant and submissive rat cortex. Expression levels of gamma synuclein were elevated consistently in all regions of cerebral cortex of dominant rats ($P < 0.05$; 23.5 +/- 1.1) in comparison to the submissive rat group (10.3+/- 1.2). Neutral rats had intermediate cerebral cortex levels of gamma synuclein expression (15.7 +/- 1.4) that were significantly lower than dominant rats ($P < 0.05$). No changes in alpha or beta synuclein expression were observed among the groups. These studies indicate that in the cerebral cortex gamma synuclein levels were differentially associated with dominant and submissive behavior and suggest that they may be markers for mania and depression.

51. COMPARISON OF RECORDINGS OF 22-kHz RAT CALLS BY DIRECT DIGITIZATION AND VIA BAT DETECTORS. Holland, G.; Brudzynski S. M. Dept. of Psychology and Centre for Neuroscience, Brock University, St. Catharines, ON, L2S 3A1 Canada. In recording ultrasonic rat calls, it is common practice to use bat detectors purported to divide the frequency spectrum in order to reduce the total bandwidth of calls prior to storage on analogue audio tape. More recently, direct digitization to disc has become available which does not rely on frequency division. 22-kHz calls were induced from adult Wistar rats by air puffs and were recorded simultaneously through two bat detectors - the D230 (Pettersson Elektronik) and the S25 (Ultra Sound Advice) – to tape, and also by direct digitization. The direct recordings were done with a Larson-Davis microphone, a Data Translations ADC board at 250 kHz sampling rate, and Signal v3.12 sound recording and analysis software package. The parallel recordings of each call were compared and quantitatively analysed for specific time and frequency characteristics. Direct recordings were practically free of noise. Aperiodic sounds such as air puffs were well characterized in direct recording but ignored by the bat detectors. While a bat detector will output a square wave at the same frequency as its input, resulting in a characteristic pattern of odd harmonics, the true harmonic structure of 22-kHz calls was elucidated by direct digitization, and was seen to include a weak 2nd harmonics. Recordings by bat detector characterized onset and offset times of calls with practically no error relative to the directly recorded times. Minimum frequencies through the bat detectors agreed adequately with minimum frequencies measured directly. Maximum frequency occurring at the onset of each call was characterized less well, and 10-20% of such measurements by either bat detector were seriously inflated. Finally, the instantaneous bandwidth (width of sonographic line) of calls was greatly widened by both bat detectors. Supported by the Natural Sciences and Engineering Research Council of Canada.

Friday, June 18

8:30-10:30 Symposium 2: Modeling abnormal brain and behavior development: When more is better

EFFECTS OF NEONATAL SEROTONIN DEPLETION ON CORTICAL DEVELOPMENT AND BEHAVIOR: A MOUSE MODEL FOR AUTISM Hohmann, C.F.; Blue, M.E*. Department of Biology Morgan State University, Baltimore MD 21251. *The Kennedy Krieger Institute, Balto. MD 21201. Autism is a neuro-developmental disorder of currently unknown etiology, characterized by a variety of behavioral abnormalities and accompanied by structural and neurochemical changes in various brain regions. Animal models are necessary to elucidate the neurobiology leading to disease characteristic pathologies but few exist for autism. We have developed a mouse model to test the hypothesis that serotonergic [5-HT] imbalances during brain development are related to increased cortical volumes observed in early postnatal autism and that these neuropathologies are the substrate for cognitive and sensory-emotional abnormalities. We have shown previously that neonatal 5, 7 dihydroxytryptamine [5, 7 DHT] injections into the medial forebrain bundle of Balb/CByJ mice, at birth, result in transient 5-HT depletions of the developing cortex and increased widths of cortical layers by adulthood. Moreover, these mice displayed impaired retention of passive avoidance behavior and improved performance on a non-matched-to-sample odor discrimination task. The present talk will focus on the development of behavioral tasks to ascertain if these neonatally 5-HT depleted mice show behaviors interpretable as autistic and we will examine what should be regarded as mouse appropriate behavior for “autism”. Moreover, we will discuss strategies to correlate structural alterations in the brain of these

mice with behavioral measures and their usefulness in illuminating the neurobiological substrate of autism. Supported by NIHNCRR-1G12RR17581, NAAR and U54 MH066417-01A1.

GENETIC MODEL FOR RETT SYNDROME. Blue, M.E. Dept. of Neurology and Neuroscience, Johns Hopkins Univ. School of Med. And kennedy Krieger Research Institute, Baltimore, MD 21205 USA. Rett Syndrome (RS) is a neurodevelopmental disorder that principally affects girls. The clinical course is characterized by a relatively normal first year followed by pronounced regression in function in the second year. After the regressive phase, patients with RS stabilize and, in some cases, improve. The large majority of cases of RS are caused by mutations in methyl-CpG binding protein (MeCP2), a gene located on the X chromosome. Previous studies have shown that MeCP2 acts to repress transcription in in vitro tissue. In the brain, immunoctytochemical studies show that MeCP2 is expressed almost exclusively in the nucleus of neurons. MeCP2 expression is ubiquitous, resembling that of Nissl-stained sections. During development, MeCP2 is expressed in postmitotic neurons and the onset of MeCP2 expression is most closely correlated with synaptogenesis. Genetic animal models for RS to date consist of mice that have varying portions of the MeCP2 gene knocked out. In many of these mouse models, the behavioral phenotype does mimic many of the features seen in patients with RS, including stereotyped hand movements and motoric deficits. In this presentation the current mouse models for RS will be discussed and the structural and functional deficits in each will be delineated. Experimental issues with these models also will be discussed.

HOW GENE-ENVIRONMENT INTERACTIONS CAN SHAPE BIOBEHAVIORAL DEVELOPMENT IN RHESUS MONKEYS. Suomi, S.J. Lab Comparative Ethology, National Institute of Child Health & Human Develoment, NIH, DHHS, Bethesda, MD 20892-7971, USA Recent research has disclosed marked individual differences in patterns of biobehavioral development exhibited by rhesus monkeys across the lifespan. For example, approximately 5-10% of rhesus monkeys growing up in the wild consistently exhibit impulsive and/or inappropriately aggressive responses to mildly stressful situations throughout development; those same individuals also show chronic deficits in their central serotonin metabolism. These characteristic patterns of biobehavioral response emerge early in life and remain remarkably stable from infancy to adulthood. Laboratory studies have demonstrated that although these characteristics are highly heritable, they are also subject to major modification by specific early experiences, particularly those involving early social attachment relationships. For example, a specific polymorphism in the serotonin transporter gene is associated with deficits in serotonin metabolism, extreme aggression, and excessive alcohol consumption among monkeys who have experienced insecure early attachment relationships but not in monkeys who have developed secure attachment relationships with their mothers during infancy.

VIRAL MODELS OF NEURODEVELOPMENTAL INJURY Mikhail Pletnikov Johns Hopkins University School of Medicine, Baltimore, MD 21205 Human developmental behavioral disorders, such as schizophrenia and autism, are complex diseases with unknown etiology. Besides genetic and non-infectious environmental factors, prenatal and early postnatal viral infections have been also implicated. Since studying the complex mechanisms of developmental abnormalities in humans is very difficult, animal models are often used to identify pathogenic events and associated neurobehavioral consequences and to search for novel therapeutic regimens. We will critically discuss advantages and limitations of viral animal models of early brain injury by presenting common and unique features of prenatal influenza virus infection in rats, neonatal influenza virus, mumps virus and Borna disease virus infections of the brain in rats. We will conclude the talk by considering new directions in modeling abnormal brain and behavior development. Supported by MH-48948.

1:30-3:30 Symposium 3: Estrogen: Old hormone, new tricks

THE ALPHA AND BETA'S OF ESTROGEN'S ACTIONS IN BRAIN Emilie F. Rissman Department of Biochemistry and Molecular Genetics University of Virginia Charlottesville, VA 22908 Since the discover of a second estrogen receptor (ERbeta) in 1996 and the development of knockout (KO) mice for each of the two ERs great progress has been made in distinguishing the roles and actions of each receptor in brain. In this talk I will give an overview of the work conducted in mice that illustrates both independent and dependent roles for each ER. Interactions between ERalpha and ERbeta will be emphasized. I will focus on behavioral studies covering a range of topics including social, sexual and cognitive behaviors. In addition I will discuss neural data suggesting that ERalpha and ERbeta regulate some estrogenic proteins in concert and others in a more exclusive manner. In general male mice lacking functional ERalpha genes exhibit a suite of behavioral responses to conspecifics that are best described as "social anxiety". Their solitary behaviors are largely unaffected by the gene mutation. Female ERaKO mice also have many behavioral deficits, including lack of sexual receptivity. Male mice without functional ERbeta delayed behavioral sexual maturity. Females exhibit receptivity but have impaired spatial learning ability. To disentangle the roles of these two receptors during development versus during adulthood the aromatase knockout (ArKO) mouse is a useful model. These mice fail to convert testosterone to estradiol. I will present sexual behavior

data from our ongoing studies with this strain and present a novel model delineating the actions of ERalpha versus ERbeta in behavior. This work is supported by NIH grants R01 MH57759 and K02 MH01349.

SOY AND SEX: THE EFFECT OF DIETARY PHYTOESTROGENS ON SEX BEHAVIOR. Heather B. Patisaul, Jordan Luskin, Adele Blum. Center for Behavioral Neuroscience, Emory University, Atlanta, GA 30329 Soy and soy supplements are rapidly increasing in popularity because of their purported health benefits, and the FDA's recent announcement that consuming 25mg of soy per day has significant cardiovascular benefits. We have discovered, however, that these supplements disrupt numerous estrogen-dependent pathways in the brain, many of which are critical for the production and regulation of sexual and anxious behaviors. Therefore we sought to determine if these supplements could disrupt these behaviors using a rodent model. The effect of a popular soy supplement on sexual receptivity and proceptivity was examined in ovariectomized adult female rats. The animals were maintained on a soy-free diet and treated with either sesame oil, estradiol benzoate (10µg, EB), tamoxifen (5 mg implant, 21 day release) the supplemented diet (3.5g/kg diet), tamoxifen with EB or the supplemented diet with EB (n = 6 per group). 48 Hours later, all groups were given progesterone injections (500µg) and testing began four hours later. Supplement treatment inhibited the lordosis response by 28% and tamoxifen treatment inhibited the lordosis response by 33% in hormone-treated animals compared to hormone-treated controls on a soy-free diet ($P < 0.001$). Similarly, proceptive behaviors, were 60% lower in hormonetreated animals on the supplemented diet ($P < 0.001$) and 30% lower in hormone-treated animals given tamoxifen implants ($P < 0.02$) compared to the hormone-treated controls. Neither tamoxifen nor the supplemented diet had an effect on any measure of sexual behavior in the absence of estrogen.

CHRONIC STRESS AND ANXIETY: SEX DIFFERENCES. Altemus, M.; Yang, R.; McEwen B.S. Department of Psychiatry, Weill Medical College, Department of Psychiatry, New York, NY 10021 USA. 21-day chronic restraint stress is known to result in a constellation of behavioral and neurobiological changes in male rats. These changes include increased expression of conditioned and unconditioned fear and suppression of hippocampal neurogenesis. These effects of 21-day restraint stress were compared among intact male rats, intact female rats, and ovariectomized females. After completion of the 21-day restaint stress, animals were tested in open field and a conditioned fear pardigm which included contextual and cues stimuli. In all three groups of animals, stress was associated with reduced wt gain and increased adrenal weight. Stressed male rats and ovariectomized female rats showed similar changes: increased contexual and cued conditioning, reduced acivity in the open field, and suppression of hippocampal neurogenesis. In contrast, intact female rats subjected to the chronic stress had no changes in fear behaviors or hippocampal neurogenesis compared to unstressed intact female rats. These results suggest that, in females, gonadal steroids protect against chronic stress-induced anxiety and suppression of neurogenesis.

ESTROGEN RECEPTORS AND THE REGULATION OF MALE SOCIAL BEHAVIOR. Cushing, B.S., Dept. of Psychiatry, University of Illinois at Chicago, Chicago, IL 606612, USA The expression of male social behaivors varies between males, with monogamous males displaying higher levels of prosocial behavior and lower levels of aggression than polygynous males. While many factors regulate social behavior, steroids, especially estrogen, acting via the estrogen receptor subtype α (ERα) play a major role in the expression of male typical social behaviors. Therefore, males that express more female typical social patterns, such as parental care, would be predicted to express significantly lower levels of ERα than males that display more typical male patterned behavior. To test this prediction the distribution of ERα was compared between males prairie voles (*Microtus ochrogaster*) from Illinois (IL), which are highly social and monogamous, and Kansas (KN), which are less social and displays some polygynous characteristics. Brains were collected from sexual-naïve IL and KN adult males and immunocytochemistry was used to visualize ERα. There were significant differences in the distribution of ERα, with IL males expressing significantly less ERα than KN males in the bed nucleus of the stria terminalis (BST) and the medial amygdala (MeA). Difference in the BST and MeA support the hypothesis, as these areas influence affiliation and aggression. To determine if ERa is directly affecting the expression of male social behavior ERα was increase in the MeA and BST in IL males using adeno-associated viral vectors containing ERα cDNA. Males then participated in a series of behavioral tests to determine the effects of increased ERα on affiliation and aggression. Increasing ERα in the MeA and BST altered the expression of prosocial behavior and increased levels of aggression, supporting the hypothesis that ERα regulates the expression of prosocial behavior in males by masculinizing male social behavior.

3:30-500 Oral Session 1: Fear and Defense

LOCOMOTION IN A DARK OPEN FIELD COMPRISES "LOOPS" OF RETURNING TO RECENT PAST PLACES. Zadicario, P.; Zadicario, E.; Avni, E.; Eilam, D. Department of Zoology, Tel-Aviv University, Ramat-Aviv 69 978, Israel. The behavior of captive wild jirds (gerbils) in a lit arena is comprised of periods of progression

that are interrupted with stops and organized as a set of round trips to a home base, as was previously shown in other rodent species. In a dark open field, however, their progression is entirely different, taking the form of diversive locomotion with no apparent structure. In this study we uncover two characteristics of progression in a dark open field. First, the rodents locomote continuously at a low speed, and the distinction between bouts of progression and stops that characterizes locomotion in lit arena disappears. Second, the structure of progression in the dark is based on Looping: the rodents move in a circular trajectory, closing their path as a loop to a recently traveled place that varies from one loop to the next. Once this mechanism was revealed, the trajectory of progression of the jirds became highly predictable. Conceptually, locomotion in the dark may be thus regarded as a set of round trips to a continuously shifting home base that in a lit open field converge to a home base by using visible environmental landmarks. We also propose that the looping mechanism may be applicable for the behavior of hippocampal rats that feature hyperactivity and diversive locomotion, reminiscent of those seen in jirds in a dark arena.

GLUCOCORTICOIDS IMPAIRS FEAR MEMORY RETRIEVAL Cai, W.; Greene, R.W. Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas VAMC, Dallas, TX. Objectives: Prior research has revealed that glucocorticoids modulate memory function. In particular, glucocorticoids enhance fear memory consolidation in an inverted U curve fashion. Here we used fear conditioning paradigm to study the effect of glucocorticoids on context and auditory cue-dependent fear memory retrieval. Methods: Fear conditioning paradigm is established by using 0.5 mA with two pairing footshock aparted 60 sec in between, and the animals were tested 24 hours later in both context and cue-dependent fashion. Results: We found that corticosterone 3.0 and 10.0 mg/kg intraperitoneal injection 30 minutes prior to the retrieval test produced significant impairment in 24 hr long-term fear memory retrieval, whereas 0.3 and 1.0 mg/kg corticosterone injection had no effect. Corticosterone injection 2 minutes prior to retrieval had no effect. This indicates that the glucocorticoid effects are not likely due to immediate action, but delayed mechanisms. This effect was not caused by corticosterone-induced change in locomotor activity or anxiety levels, because 3.0 mg/kg corticosterone injection had no effect when injected 30 minutes prior to the open field and elevated plus maze tests. All the serum levels of glucocorticoids were measured and recorded accordingly, indicating the 3.0 and 10.0 mg/kg corticosterone injection prior to the retrieval test did produced significant increase in serum corticosterone levels. Conclusions: These data support the hypothesis that glucocorticoids can directly impair fear memory retrieval selectively without altering motor coordination, sensation, locomotor activity or general anxiety levels.

ACTIVATION OF NADPH-DIAPHORASE POSITIVE NEURONS AFTER EXPOSURE TO A LIVE CAT. Beijamini, V; Guimaraes, FS. Dept. of Pharmacology, Medical School, University of Sao Paulo, Ribeirao Preto, Brazil. NO may have an anxiogenic role. Several regions related to defensive reactions contain nitric oxide synthase (NOS) immunreactive neurons. NADPH-diaphorase (NADPHd) activity can be used to detect the presence of NOS neurons. Objective: To investigate if NOS positive neurons are activated after exposure to an innate fear stimulus. Methods: Male Wistar rats (230-250 g, n=4-8/group) were exposed to a live cat for 10 min. Exposure to a toy cat was used as control. Two hours later, the brains were removed and processed for c-Fos immunohistochemistry and NADPHd histochemistry. Double-stained (DS, c-Fos+NADPHd positive neurons) cells were represented as percentage of NADPHd positive cells. Results: Cat exposure significantly ($p<0.05$) increased DS cells in the parvocellular paraventricular hypothalamic nucleus (pPVN, cat=29±5; control=9±6), lateral hypothalamic area (LH, cat=22±2; control=14±2), dorsolateral periaqueductal grey (dlPAG, cat=15±1; control=6±1), dorsal raphe nucleus (DRN, cat=19±3; control=6±3) and bed nucleus of stria terminalis (BNST, cat=54±20, control=0±0). Fos-like Immunoreactivity (FLI) increased in the pPVN, LH, dlPAG, DRN, medial amygdaloid nucleus, lateral amygdaloid nucleus, BNST, cingulated cortex. There were no significant differences in the magnocellular PVN, inferior colliculus, basolateral amygdaloid nucleus, paraventricular thalamic nucleus. No difference in the absolute number of NADPHd neurons was found in any region. Conclusion: The results suggest that exposure to an innate fear stimulus such as a live cat activates NOS positive neurons in some brain regions related to defensive reactions.

THE SECURITY-MOTIVATION HYPOTHESIS OF OCD. Szechtman, H.; Woody, E.Z. Dept Psychiatry & Behavioural Neurosciences, McMaster Univ and Dept Psychology, Waterloo Univ. Szechtman and Woody (2004) hypothesized that obsessive-compulsive disorder (OCD) results from a deficit in the feeling of knowing (termed *yedasentience*) that normally terminates thoughts or actions elicited by security motivation. To test the plausibility of this proposed mechanism, an experiment was conducted to produce an analog of OCD washing by eliciting a scenario of potential harm and using hypnosis to block changes in internally generated feelings that would normally occur during washing. Participants reacted with increased disgust, anxiety, and heart rate to their mental images of contamination and potential danger. As predicted, high but not low hypnotizable participants showed a significant prolongation of washing when change in feelings during washing was blocked hypnotically. Results are consistent with the proposed model that an affective signal terminates security motivation and that a deficit in this motor-generated yedasentience satiety signal will lead to prolonged performance of security motivation species-typical behaviors, characteristic of OCD symptoms. H. Szechtman and E. Woody. Obsessive-compulsive disorder as a disturbance of security motivation. *Psychological Review* 111 (1):111-127, 2004.

5:00-7:00 Poster Session 2

Memory II

52. ESTROGEN, BUT NOT ESTROGEN PLUS PROGESTERONE, ENHANCES MEMORY CONSOLIDATION IN AGED FEMALES. Levy, L.J.; Bennett, J.C.; Frick, K.M. Dept. of Psychology, Yale Univ., New Haven, CT, USA. Although estrogen can reduce memory decline in menopausal women, recent data suggest that the addition of progesterone to estrogen treatment is detrimental to memory. However, the interpretation of these data are complicated by the fact that little is known about the effects of progesterone on memory. The present study sought to determine whether estrogen alone or estrogen plus progesterone affect memory consolidation in ovariectomized aged (22 months) female C57BL/6 mice. In Exp. 1, mice were trained for 8 trials in a spatial Morris water maze task and immediately afterwards, received i.p. injections of 17ß-estradiol (E_2,; 0.1, 0.2, or 0.4 mg/kg) or vehicle (VEH). Mice were re-tested 24 hrs later. All mice learned to find the platform on day 1. On day 2, the VEH, 0.1 mg/kg E_2, and 0.4 mg/kg E_2 groups displayed forgetting of the platform location, whereas the 0.2 mg/kg E_2 group did not forget overnight. In Exp. 2, a new set of mice was injected after water maze training with 0.2 mg/kg E_2 combined with 5, 10, or 20 mg/kg progesterone. Progesterone reduced estrogen's ability to enhance spatial memory consolidation. Neither hormone affected a non-spatial water maze task. The data indicate that estrogen can improve spatial memory consolidation in aged females and that progesterone attenuates estrogen's beneficial effects. (Supported by Yale Univ. and NIMH grant MH065460).

53. LONG-TERM CONTINUOUS, BUT NOT DAILY, ENRICHMENT REDUCES SPATIAL MEMORY DECLINE IN AGED MALE MICE. Bennett, J.C.; McRae, P.A.; Levy, L.J.; Frick, K.M. Dept. of Psychology, Yale University, New Haven, CT, 06520 USA. Environmental enrichment (stimulation provided by conspecifics, rodent toys, and running wheels) attenuates memory decline and increases synaptic plasticity in aging rodents. However, it is unclear whether all enrichment treatments improve memory similarly because effects of different enrichment conditions on memory have never been examined. Thus, the present study investigated in aged (23 months) male C57BL/6 mice the effects on memory in the Morris spatial water maze (MWM) and water-escape motivated radial arm maze (WRAM) of 3 enrichments conditions: daily handling, daily enrichment for 3 hrs/day, or continuous enrichment in the home cage. Young control (YC; 4 months) and aged control (AC) mice lived in shoebox cages with up to 5 mice. Other aged males were divided into 3 enrichment conditions for 4 weeks prior to and during behavioral testing: 1) daily handling for 5 minutes (aged daily handling, ADH), 2) daily placement in a large cage with a running wheel and rodent toys for 3 hrs (aged enriched daily, AED), 3) housing in a giant cage with up to ten mice and continuous exposure to many running wheels and toys changed twice/week (aged enriched continuously, AEC). YC and AEC animals performed better than all other groups in the MWM. In the WRAM, YC and AEC mice made fewer spatial reference memory errors compared to the remaining groups, and the AEC group made fewer spatial working memory errors than ADH and AED groups. These findings suggest that only certain types of enrichment prevent memory decline in aged males. (Supported by Yale University, American Federation for Aging Research/Pfizer, and NIMH MH065460).

54. EFFECT OF CHRONIC OLANZAPINE ON SPATIAL MEMORY AND LOCOMOTOR ACTIVITY IN RATS WITH HIPPOCAMPAL LESIONS. McNutt, C.T.; Gowdy, J.C.; O'Connell, S.M.; Bardgett, M.E. Department of Psychology, Northern Kentucky University, Highland Heights, KY 41099 Many animal studies have demonstrated that damage to the hippocampus impairs spatial memory and elevates spontaneous locomotor activity. These behavioral changes may be analogous to the memory deficits and agitation observed in clinical disorders marked by hippocampal dysfunction, such as Alzheimer's disease and schizophrenia. These disorders are commonly treated with antipsychotic drugs, and many recently developed, atypical antipsychotic drugs may possess cognitive-enhancing properties in addition to serving as effective antipsychotics. The purpose of this study was to determine if one of these newer drugs, olanzapine, could improve memory and normalize locomotor activity in rats with hippocampal damage. Adult male Sprague-Dawley rats received NMDA or sham lesions of the dorsal hippocampus. Seven days after surgery, half of the animals in each lesion group received daily injections of saline, while the other half received daily injections of 0.5 mg/kg of olanzapine for the remainder of the experiment. Animals were tested for locomotor responses to a novel environment two weeks later. Hippocampal lesions were found to increase locomotor activity, but olanzapine treatment reduced this lesioned-induced activity to control levels. Animals were then tested in a food-motivated delayed spatial alternation task. Hippocampal lesions impaired performance in this task and this lesion effect was not reversed by daily olanzapine treatment. These data suggest that changes in locomotor activity produced by hippocampal lesions are sensitive to olanzapine treatment, but lesion-induced memory deficits are not. Further investigation of other doses or dosing regimens of olanzapine will be needed in order to fully appreciate its effect on memory and activity in the context of hippocampal damage. Supported by

grants from the NKU Center for Integrative Natural Sciences and Mathematics and the Kentucky Biomedical Research Infrastructure Network.

55. CPEB NULL MICE DISPLAY ALTERED SPATIAL NAVIGATION REVERSAL LEARNING. Terry, R.; Stearns, N.; Yang, R.; Richter, J.; Berger-Sweeney, J. Dept. Biology, Wellesley College, Wellesley, MA 02481; Program Molecular Biology, UMass Med. Worcester, MA 01605 USA. Activity-dependent local translation of dendritic mRNAs may underlie synaptic plasticity. The cytoplasmic polyadenylation element protein (CPEB) promotes cytoplasmic polyadenlation in dendrites in response to synaptic stimulation. CPEB controls synaptic translation of CaMKII mRNA, which is needed for the maintenance of LTP, and it is enriched in the postsynaptic density. We hypothesized that loss of CPEB would alter learning and/or memory of a spatial task. Wildtype and null mice performed acquisition, reversal, reacquisition, and extinction of a spatial navigation task, as well as a cued navigation task. Here we report that CPEB null mice display altered rates of reversal learning, despite normal acquisition and extinction of the spatial navigation task. Cued performance was similar in the wildtype and null mice, suggesting similar motivation and motoric and visual abilities in the two groups. These data suggest that synaptic activation may drive local translation in the dendrite and may be critical for the acquisition of spatial information.

56. DEFICIT OF DIFFERENT ASPECTS OF SPATIAL MEMORY IN TG2576 TRANSGENIC MICE AS A MODEL OF ALZHEIMER'S DISEASE.Ognibene, E 1; Middei, S 2; Daniele, S 2; Ghirardi, O 2; Caprioli, A 2; Laviola, G 1.1 Department of Cell Biology & Neuroscience, Istituto Superiore di Sanita', Roma, Italy. 2 Behavioural Pharmacology Lab, Sigma-Tau SpA, Pomezia, Italy Deficit of different aspects of spatial memory in Tg2576 transgenic mice as a model of Alzheimer's disease. Transgenic mouse models of Alzheimer's disease have been recently advanced. Among them, the Tg2576 mice develop progressive increasing of Aß peptide levels, and exhibit impairment of cognitive function. Aim of this study was to better characterize different aspects of spatial memory performance of transgenic mice, observed when Aß neurotoxic peptides reached high levels. A generalized elevation of basal locomotory activity was found in Tg2576 mice, which was associated with an impairment in Y-maze spontaneous alternation. In the cross-maze test, Tg2576 mice produced faster performances (index of a more rapid routine-oriented organization of motor responses) during the training period. However, Tg2576 mice were not flexible upon changes in the schedule and failed to codify spatially the testing environment. Consistently, when assessed for levels of reactivity to spatial change in the modified open-field test with objects, a deficit of spatial memory was observed. Compared to controls, Tg2576 mice also exhibited an increased number of explorative approaches to the different objects, and failed to discriminate the displacement of the object. Results clearly indicate that Tg2576 mice are characterized by a number of specific behavioral cognitive alterations, compatible with Alzheimer's disease (AD), which make them a suitable animal model for testing of novel anti-AD drugs.

57. INDIVIDUAL DIFFERENCES IN WATER MAZE PERFORMANCE AND OPEN FIELD BEHAVIOR IN AGED AND ADULT RATS. Topic, B.; Jocham, G.; Kart, E.; Schulz, D.; De Souza Silva, M.A.; Huston, J.P. Institute of Physiological Psychology and Center for Biological & Medical Research, University of Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany The aim of the present study was to examine the nature of individual differences in behavior in adult as compared to aged rats in the Morris water maze task. For this purpose animals were trained in the "hidden platform place learning version" (3 trials/day except for the first day, which consisted of 4 trials) followed by 8 extinction trials given over 3 days, and classified into superior and inferior learners according to their performance during water maze acquisition. Performance during acquisition was related to extinction parameters in the water maze as well as to exploration parameters in an open field. As expected, differences between adult and aged animals were found in most of the measured variables. Unexpectedly, performance in the water maze was highly related to the amount of thigmotactic behavior, independent of age, and correlated with rearing behavior in the open field. The differences found in behavioral measures between inferior and superior performer subgroups were invariant across age; the inferior adult and aged subgroups exhibited similar behavioral characteristics, and the same was true for the adult and aged superior subgroups. It was found that animals defined as inferior and superior performers on the basis of escape times during acquisition in the water maze can be differentiated on the basis of characteristics of (a) thigmotactic swimming during different phases of the water maze and (b) exploratory behavior in the open field.

58. α7 NICOTINIC RECEPTOR ANTISENSE IMPAIRS PERFORMANCE IN THE MORRIS WATER MAZE AND DECREASES MLA BINDING. Curzon, P.; Anderson, D.J.; Nikkel, A.L.; Gopalakrishnan, M.; Decker, M.W. & Bitner, R.S. Neuroscience Research, Abbott Laboratories, Abbott Park, IL 60064-3500, USA. In the rodent CNS, nine genes encode a family of α and β subunits (α2- α7, β2- β4) that assemble to form neuronal nicotinic receptors (NNRs). Studies have demonstrated that nicotine and NNR agonists enhance learning and memory while NNR antagonists can impair performance. Studies involving CNS administration of the α7 NNR antagonist, methyllycaconitine (MLA), have shown deficits in spatial working memory. However, studies with α7 NNR knockout mice failed to detect any impairment in a variety of learning paradigms. In the present study, an antisense

oligonucleotide (aON) approach was utilized to investigate the effects of α7 NNR knockdown on spatial learning and memory. Rats receiving repeated i.c.v. injections of an aON that was shown to reduce α7 mRNA expression in PC12 cells exhibited impaired spatial learning and memory in the Morris Water Maze paradigm. Specifically, aON treatment significantly impaired acquisition across training days 2-4 and performance during the probe trial on day 5 as compared to control oligomer and saline-injected animals. Following testing, [^{3}H]-MLA binding in the hippocampus and frontal cortex revealed significant reductions in α7 NNR binding (42% and 25%, respectively). The present study provides novel evidence of the role of α7 NNRs in spatial learning and memory.

Anxiety and Fear

59. NEUROTOXIC LESIONS OF THE DORSAL AND VENTRAL HIPPOCAMPUS IMPAIR ACQUISITION AND EXPRESSION OF TRACE CONDITIONED FEAR-POTENTIATED STARTLE. M.A.TRIVEDI and G.D. COOVER, Northern Illinois Univ., DeKalb, IL 60115. In trace fear conditioning a conditioned stimulus (CS) is followed by a stimulus-free time interval before the unconditioned stimulus (US). The hippocampus is critical for trace conditioning, and electrolytic lesions of the DH, but not the VH significantly impair acquisition of trace conditioned fear-potentiated startle (FPS) (Coover & Trivedi, 2003). The present experiments compared the effects of NMDA lesions to the DH and VH on acquisition and expression of trace FPS in male, albino rats. Fear conditioning sessions consisted of 3 daily sessions of 15 trials in which a 3.8-s noise CS was followed after a 6-s trace interval by a 0.5-s footshock of 0.6 mA intensity. Pre-training lesions of the DH or VH were made prior to the first training session and post-training lesions were made 1 day after the last training session. Trace FPS was defined as the difference in magnitude of startle 6 s after CS offset compared to baseline startle during the intertrial interval. Both VH and DH lesions impaired acquisition and expression of trace FPS. These results support prior studies indicating a role for the hippocampus in trace conditioning. However these results fail to support the notion that there are functional differences between the DH and VH in trace FPS.

60. THE ROLE OF BOMBESIN-LIKE PEPTIDES IN FEAR-POTENTIATED STARTLE. Mountney, C[1]., Bedard, T[1]., Mennie, K[1]. & Merali, Z[1,2]. [1]Dept. of Psychology, [2]Institute of Mental Health Research, University of Ottawa, Ontario, Canada. Our previous research suggests the involvement of two mammalian Bombesin (BB)-like peptides, gastrin-releasing peptide (GRP) and Neuromedin B (NMB) in stress and/or anxiety responses. This study assessed the role of GRP and NMB and their respective receptors (BB_2 and BB_1) in learned fear using a Fear-Potentiated Startle Paradigm. Animals were injected with either GRP, GRP antagonist (GRPa), NMB, NMB antagonist (NMBa) or vehicle, and were exposed to a startle-provoking stimulus (110db white noise) in the absence or presence of a cue (tone) previously paired with shock. Results show that as compared to the control condition, GRPa appears to increase the fear-potentiated startle response, whereas NMBa decreases fear-potentiated startle. Taken together, these results provide evidence supporting the view that BB_1 and BB_2 receptors may have distinct (opposing) effects on the expression of fear and/or anxiety responses. This study provides a broader framework for the study of the involvement of these peptides in stress and anxiety responses.

61. EFFECTS OF GASTRIN-RELEASING PEPTIDE AND NEUROMEDIN B ON LEARNED FEAR & ANXIETY. 1Bédard, T., 1Mennie, K., 1Mountney, C., 3Anisman, H. & 1,2Merali, Z. 1University of Ottawa, School of Psychology; 2University of Ottawa, Institute of Mental Health Research; 3 Carleton University, Neuroscience Institute. Bombesin (BB) appears to elicit effects akin to the stress response. This study examined the role of Gastrin Releasing Peptide (GRP) and Neuromedin B (NMB), mammalian BB-like peptides, in fear and anxiety-type responses. Rats were randomly assigned to one of five drug groups, GRP, GRP antagonist (GRPa), NMB, NMB antagonist (NMBa) or control (vehicle). Their effects on anxiety were first assessed using the Elevated-Plus Maze (EPM) and Open Field paradigms (OF). Subsequently, effects on the Conditioned Emotional Response (CER) were assessed. This test evaluated fear expression, fear extinction and memory reconsolidation processes. Animals were first conditioned to fear the context (shock cage) or cue (tone) by pairing them with a footshock. Results show that in the OF, both peptide antagonists appeared to have anxiolytic effects whereas the agonists tended to be anxiogenic. In the EPM, NMBa was shown to decrease anxiety, whereas the other treatments were without significant effect. In the CER paradigm, contextual fear was attenuated by NMB and less so by GRP. However, GRPa appeared to enhance the expression and recall of cue provoked fear. During the extinction test, fear expression was lower, and animals that had initially received GRPa showed higher levels of fear expression. It can be concluded that although GRP and NMB are structurally related, they appear to have very distinct effects on the expression of anxiety versus fear-type responses. Thus, these peptidergic systems represent novel targets for pharmacotherapy of stress-related

62. THE HABENULA COMPLEX MEDIATES EXPERIENCE-DEPENDENT REGULATION OF MONOAMINE SYSTEMS. Heldt, S.A.; Ressler, K.J. Center for Behavioral Neuroscience. Emory University, Atlanta, GA 30329 USA. The function of the habenula complex in behavior is not well understood, but it is known to modulate the activity of dopaminergic and serotonergic systems which has led to its implication in psychiatric

illnesses. Here we report that genes that have been implicated in schizophrenia, such as ErbB4, substance P, neurotensin receptor, and nicotinic acetylcholine receptors are highly expressed within the habenula. We found that following conditioned fear stress, the habenula shows enhanced expression of the neural plasticity genes fos, actinin, nurr-1, and neurofilament. Discrete bilateral lesions of the habenula have no initial effect on behavior. However, following conditioned fear stress, habenula-lesioned mice show a relative reduction in prepulse inhibition that is long-lasting and is temporarily reversible with the dopaminergic / serotonergic antipsychotic clozapine. Habenula animals also show enhanced apomorphine-induced activity. Furthermore, they have reductions in GAD67 and increases in EAAC1 gene expression in several brain areas which is consistent with clinical findings of altered GABAergic and glutamatergic tone in psychotic disorders. Together, these data suggest that the habenula may play an integral role in experience-dependent regulation of brainstem monoamine systems, and that alteration of these systems may lead to global alterations in fast neurotransmitter circuitry. Such abnormalities in humans could contribute to psychotic disorders such as schizophrenia.

63. LINKS BETWEEN TEMPERAMENT DIMENSIONS AND BRAIN MONOAMINES IN THE RAT. Hansen, S.; Ray, J.; Waters, N*. Department of Psychology, Göteborg University, Sweden; *Carlsson Research AB, Göteborg, Sweden Our previous work on rats has shown that there are large and stable individual differences in behaviors reflecting harm avoidance and novelty seeking. In the present work we searched for associations between these temperamental traits and the monoamine levels measured in ten different brain regions. Using a multivariate regression method (PLS), high harm avoidance scores were associated with low levels of striatal dopamine, and with high levels of cortical norepinephrine and amygdala 5-HIAA. High novelty seeking scores were linked to low levels of brainstem 5-HT and dopamine, and to low levels of 5-HIAA in amygdala and accumbens. Moreover, rats scoring high on novelty seeking had higher-than-average levels of norepinephrine in the amygdala and thalamus, and of 5-HT in the amygdala. Together, the neurochemical predictors accounted for about 60% of the temperamental variation. Supported by the Swedish Research Council.

64. V1aR EXPRESSION IN THE LATERAL SEPTUM IS NECESSARY AND SUFFICIENT FOR SOCIAL RECOGNITION IN MICE: A KNOCKOUT AND GENE REPLACEMENT STUDY. *Bielsky, I.F.; †Hu, S-B.;*Young, L.J. *Department of Psychiatry and The Center for Behavioral Neuroscience. Emory University, Atlanta, GA 30329 USA. †Laboratory of Mammalian Genes and Development. NICHD, NIH, Bethesda, MD 20892 USA. Considerable evidence suggests that arginine vasopressin (AVP) is critically involved in the regulation of many social and non-social behaviors, including emotionality. We have previously reported that male mice with a null mutation in the V1a Receptor (*V1aR*) exhibit markedly reduced anxiety-like behavior and a profound impairment in social recognition. We used a viral vector mediated gene transfer approach to determine where V1aR acts to affect such behaviors. Re-expression of the V1aR into the lateral septum of V1aR knockout mice (V1aRKO) resulted in a complete rescue of social recognition using the habituation/dishabituation paradigm ($p < 0.001$). V1aR re-expression did not affect anxiety-related behavior in the V1aRKO. Furthermore, over-expression of the V1aR into the lateral septum of WT mice resulted in a potentiation of social recognition behavior by significantly increasing the duration of social memory, using the social discrimination paradigm ($p < 0.001$). The over-expression of the V1aR in WT mice resulted in a mild increase in anxiety-related behavior (one-tailed, $p < 0.05$). These findings suggest that viral vector gene transfer in combination with knockout technology is an effective and innovative tool for investigating the behavioral effects of localized gene expression in the brain; and specifically that V1aR expression in the lateral septum is necessary and sufficient for normal social recognition in mice.

65. ANXIETY LEVELS IN ADULT MICE THAT EXPERIENCED REPETITIVE ACUTE PAIN IN INFANCY VARY WITH AGE AND TESTING PARADIGM. Mochinski, A. ; Schellinck, H. Department of Psychology, Dalhousie University, Halifax, Nova Scotia, Canada, B3H 4J1. The long-term behavioural effects of repetitive acute inflammatory pain experienced by rodents during early development continue to be unclear. To further investigate this phenomenon, we compared the performance of CD1 mice that had received formalin or sham injections on PND 3-5 in the elevated plus maze, light-dark box and open field apparatus. Compared with sham animals, mice that had experienced early pain, had significantly fewer head dips, more stretch attends, more open arm avoidance and more line crosses. Moreover, formalin injected mice had more head dips and more open arm avoidance and more line crosses when tested at a younger age. In comparison, when tested in the light-dark box, the formalin injected animals avoided the light less and on days 45 and 60 had more line crosses than sham controls. In the open field test, both formalin injected and sham animals showed fewer line crosses and rearing behaviours with increasing age. In general, these results suggest that both the type of test and the age of testing are two variables that must be taken into account when assessing the influence of early pain experience on later anxiety in mice.

66. EFFECTS OF A MEDITATION PROCEDURE ASSOCIATED TO RESPIRATORY EXERCISES (SIDDHA SAMADHI YOGA- SSY) IN VOLUNTEERS WITH ANXIETY COMPLAINTS- Kozasa, E.H.; Krshnam L.I., Mohandas, S.; Desideri, A.V.; Rueda,A.D.; Silva,A.A.B.; Martins,I.; Leite,M.P.; Mendes,L.; Leite, J.R. Dept. of Psychobilogy, UNIFESP (Universidade Federal de São Paulo), São Paulo, SP, BRAZIL. OBJECTIVE: Evaluate a

meditation procedure associated to breathing exercises (Siddha Samadhi Yoga- SSY) in volunteers with anxiety complaints. INTERVENTION: The subjects were submitted in one of four groups: Siddha Samadhi Yoga – SSY (respiratory exercises and meditation), meditation only, respiratory exercises (pranayamas) only, or a control group (no procedure). They were evaluated before and after three months of training, using: STAI (State and trait anxiety inventory), Beck Depression Inventory, analogic scales for subjective feelings of tension and well being, memory and attention tests. RESULTS: A significant reduction on state and trait anxiety were obtained in breathing exercises (pranayamas) group; an improvement on attention was observed specially in meditation group; a possible reduction of depression symptoms was noted too in experimental groups when compared to control group. No changes in memory testes were observed. The values were compared before and after three months of training. All experimental groups reported benefits from the practices. CONCLUSIONS: The results indicate that meditation and breathing exercises produce different benefits, and that Siddha Samadhi Yoga can be effective to relief anxiety symptoms.

Anxiety II (Plus Maze)

67. EFFECTS OF AMYGDALAR OPIOID RECEPTORS IN ANXIETY-LIKE AND CONDITIONED FREEZING BEHAVIOR IN MALE RATS. Burghardt, PR; Wilson, MA. Dept. of Pharmacology, Physiology, & Neuroscience. University of South Carolina School of Medicine, Columbia, SC 29208 USA. A growing body of literature has suggested an interaction between central opioid receptors and the actions of anxiolytic compounds. These experiments examined the role of amygdalar opioid receptors in tests of anxiety-like and context-conditioned fear behavior, and the anxiolytic actions of ethanol. The influences of highly localized injections of the nonselective opioid receptor antagonist Naltrexone (NAL) into either the central nucleus or basolateral nucleus of the amygdala were compared. Rats were bilaterally fitted with cannula aimed at the central nucleus (CeA) or basolateral nucleus (BLA) of the amygdala. Seven days after surgery rats amygdalar injections of NAL (15µg in 0.3 µl) or saline, immediately followed by a systemic injection of ethanol (1.0g/kg) or saline, before being tested in the elevated plus maze (EPM). Two days after testing in the EPM, rats received microinjections of NAL or saline before acquisition or expression of contextual fear conditioning. Preliminary data suggest that microinjections of NAL into the BLA affect open arm behavior in the EPM, but not the anxiolytic effects of ethanol. Microinjections of NAL into the CeA, however, had no effect on EPM behavior or the anxiety-reducing effects of ethanol. Further, microinjections of NAL into the BLA attenuated the expression of contextual conditioned freezing behavior. Microinjections into the CeA had no effect on the acquisition or expression of contextually paired freezing. These findings implicate opioid receptors in the BLA, but not CeA, in the behavioral responding to a novel environment and contextual conditioned fear and suggest a role for opioid receptors in the recognition of environmental factors that elicit fear responses/defensive behavior in rats. Support: RO1 MH63344 to MAW.

68. PREGNANCY AND CHANGES IN ANXIETY LEVELS IN WISTAR RATS Faturi ,C. B. (b); Teixeira-Silva ,F. (a) ; Leite, J. R. (b) (a) Universidade Federal de Sergipe, Departamento de Fisiologia, Sergipe, Brazil. (b) Universidade Federal de São Paulo, Departamento de Psicobiologia, São Paulo, Brazil. During pregnancy in mammals, concentrations of allopregnanolone (AlloP) and tetrahydrodeoxicorticosterone (THDOC) are high in the plasma and the central nervous system, due to the very high levels of their precursors progesterone and deoxycorticosterone, respectively. Both Allo and THDOC directly regulate the functions of GABA receptors manifesting GABA-agonistic properties. So, in theory, during pregnancy, interaction between the high level of these steroids and GABA receptors could lead to important psychophysiological alterations, such as a decrease of anxiety. To test this hypothesis, the levels of experimental anxiety during pregnancy in female Wistar rats were studied using a plus-maze. The animals were tested on the 7th and the 14th days of pregnancy and their results were compared with those of a control group of ovariectomized females. A significant increase in the time spent in the open arms, without a decrease in the total number of entries, was observed in the 14 day-pregnant rats in comparison to the ovariectomized control group, indicating a reduction in anxiety. Further studies including plasma measurements of Allo and THDOC are still to be performed in our lab in order to verify the correlation between the levels of these steroids and anxiety during gestation. Nevertheless, as we hypothesized, our present results clearly demonstrate a pregnancy-induced anxiolysis, a physiological phenomena which might have a role in reducing the risk of spontaneous abortions.

69. CHRONIC UNPREDICTABLE STRESS INDUCES ANXIETY-LIKE BEHAVIORS IN THE DEFENSIVE BURYING PARADIGM, BUT NOT THE ELEVATED PLUS MAZE. Karney, J.J.; Klasinski, J.L.; Matuszewich, L. Dept of Psychology. Northern Illinois University, DeKalb Il, 60115. Stress has been proposed as a contributor to several psychological disorders, such as anxiety and depression. In rodents, the defensive burying paradigm (DB) and the elevated plus maze (EPM) has been used to assess anxiety-like behaviors following exposure to stress and during abstinence from drugs of abuse. The present study investigated whether 10 days of exposure to unpredictable stress alters anxiety-like responses after the stress paradigm is terminated. We hypothesized that rats exposed to

stress would show an increase in anxiety-like behaviors and that these behavioral changes would persist following the cessation of the stress protocol. The experimental group was exposed to a chronic unpredictable stress paradigm (CUS), while the control group was handled daily for the 10 days. Animals were then tested 1 or 7 days following termination of the stress protocol in the EPM and DB. Rats exposed to the CUS protocol showed a marked decrease in latency to bury at 1 day post-stress, $t(24) = 3.21$, $p < .05$, while at 7 days post-stress rats exposed to CUS showed increased time spent burying, $t(24) = 2.37$, $p < .05$. No significant differences were found for any of the groups on the EPM. The data from this study suggests that exposure to CUS produces changes in anxiety-like behaviors in response to the noxious shock stimuli applied in DB, but not to a more generalized anxiety situation in the EPM. The increase in burying behaviors persisted following the cessation of the CUS, suggesting that stress-induced changes in the brain may endure over time.

70. TEMPORARY INACTIVATION OF THE DORSAL PERIAQUEDUCTAL GRAY MATTER REINSTATES THE ANXIOLYTIC-LIKE EFFECT OF MIDAZOLAM IN THE ELEVATED PLUS-MAZE TRIAL 2 IN RATS. Carobrez, AP*; Bertoglio, LJ; Anzini, C; Lino-de-Oliveira, C. Departmento de Farmacologia/UFSC, Florianópolis, SC, 88040-900, Brazil. *E-mail: adepadua@farmaco.ufsc.br. Rodents previously experienced in the elevated plus-maze (EPM) Trial 1, no longer respond to anxiolytic-like drugs during retesting (Trial 2). Based on the fact that the dorsal periaqueductal gray matter (dPAG) modulates fear/anxiety-like behavior, the present study sought to examine the role of this brain region in mediating this phenomenon. In order to address this issue, rats received within the dPAG, a single injection of lidocaine, a drug which produces a reversible functional inactivation, pre-Trial 1, post-Trial 1 or pre-Trial 2. Before Trial 2, all subjects received a systemic injection of midazolam and were submitted to the EPM apparatus. Data showed that 0.25 mg/kg midazolam increased the percentage of open-arm time exploration (from 15 ± 3 to 41 ± 5 %), suggesting an anxiolytic-like effect in EPM-naive rats. EPM-experienced subjects only displayed a similar pattern of results when lidocaine was administered intra-dPAG pre-Trial 2 (from 10 ± 3 to 30 ± 9 %), but not pre- (from 5 ± 1 to 7 ± 2 %) or post-Trial 1 (from 8 ± 3 to 11 ± 4 %). These effects were observed in the absence of changes in enclosed-arm entries, an EPM general exploratory activity index. The present data suggest that the increased activity in the dPAG is one possible underlying mechanism for the impaired anxiolytic-like effect of drugs in rodents previously submitted to the EPM. Research supported by: CAPES, FAPESP, CNPq, FUNCITEC-SC

71. DOES ORAL ADMINISTRATION OF GRIFFIONIA SEED EXTRACT REDUCE VOLITIONAL ALCOHOL CONSUMPTION AND ANXIETY?, Parker, J.L.; Caldwell, S.L.; Haven, K.E.; Hollen, S.G., James, N.L.; Williams, H.L.; McMillen, B.A. Dept. of Pharmacol. & Toxicol., Brody School of Medicine, East Carolina Univ., Greenville, NC 27858 As increasing numbers of patients augment their medical treatment with alternative medicines, it is necessary to examine the usefulness that many manufacturers claim for their preparations. In this study, the effects of griffonia seed extract (GSE; 99+ % 5-hydroxytryptophan), which is promoted as a sleep aid, were examined in the Myers' HEP rat for reduction of alcohol consumption and anxiety. Male rats were screened for alcohol preference by a 10-day step-up test of 3%-30% (v/v) alcohol versus tap water to determine the concentration of alcohol that resulted in an about equal consumption of alcohol solution and water. After consumption of alcohol stabilized, the rats had either 25, 50 or 100 mg/kg GSE administered b.i.d. for 3-days alone or with the peripheral decarboxylase inhibitor, benserazide, mixed into a 'chocolate biscuit' for oral consumption. Anxiety was tested in female HEP rats on the elevated plus maze: duration and latency on open arms and total arm frequency were recorded. A single dose of GSE, alone or combined with benserazide, failed to demonstrate an acute anti-anxiety effect or cause a reduction in volitional consumption of alcohol. A dose of 2.5 mg/kg of amperozide p.o. reduced alcohol consumption and a dose of 3.0 mg/kg alprazolam increased activity on the elevated plus maze. These data indicate that either insufficient amounts of 5-hydroxytryptophan enter the brain after oral administration or that an acute increase in serotonergic function does not alter these behaviors. The oral administration of GSE may be of limited value. (Suppt. by UNC Institute on Nutrition)

72. ANXIOLYTIC ACTIVITY OF ERYTHRINA VELUTINA – AN ENDEMIC PLANT OF NORTHEASTERN BRAZIL. Teixeira-Silva, F.; Alves, M.F.S.; Marchioro, M. Department of Physiology. Universidade Federal de Sergipe, Brazil. Recent studies indicate that Anxiety Disorders are the most prevalent psychiatric diseases in the general population. However, the psychotropic drugs most widely used for the relief of anxiety symptoms can either produce significant side effects, such as dependence and withdrawal symptoms, or present a delay in the onset of action. These facts have justified a considerable number of recent studies to develop new drugs for the control of these disorders. In this context, medicinal plants are of particular importance as the WHO recommends their use, especially in underdeveloped and developing countries. In Brazil, the genus Erythrina is cited in folk medicine for the treatment of nervous system excitation, insomnia, convulsions and nervous coughs. Despite this, only a few scientific studies on the pharmacological actions of Erythrina spp have been performed. In our lab, the effect of the alcohol extract from Erythrina velutina leaves was evaluated in rats in the elevated plus-maze. At a dose of 20mg/kg (p.o.), E. velutina significantly increased the percentage of entries into the open arms of the maze, and this increase was no different from that elicited by diazepam (2mg/kg – i.p.). This result suggests an acute anxiolytic activity of

E. velutina, which added to the already reported anxiolytic effect of E. mulungu (native of Southern Brazil), gives some scientific support to the use of these plants in folk medicine.

73. MICROINFUSIONS OF 8-OH-DPAT INTO THE VENTRAL HIPPOCAMPUS PRODUCE ANXIETY IN THE ELEVATED PLUS-MAZE IN MICE. [1]Fachini, G.; [1]Reis, L.M.; [2]Nunes-de-Souza, R.; [1]Canto-de-Souza, A. [1]Dept Psychology (LPA)-UFSCar/São Carlos, [2]Pharmacol, FCF-Unesp/Araraquara, Brazil. Objective: We have recently demonstrated that microinjections of WAY-100635 (a selective 5-HT1A receptor antagonist) into ventral hippocampus (VH) produce anxiolytic effects in the elevated plus-maze (EPM) in mice (Brain Res., v.927, p.87-96, 2002). This study investigated the effects of intra-VH injections of 8-OH-DPAT, a 5-HT1A receptor agonist, on anxiety in the EPM in mice. Method and Results: 4-5 days after cannula implantation in the VH, mice (n=8-10/group) received intra-VH injection of vehicle (0.1 µl) or 8-OH-DPAT (5.6 or 10 nmol/0.1 µl) and were exposed in the EPM for 5 min. The following behaviors were analyzed: number of closed arm entries (CE), a measure of locomotor activity, and percentage of open arm entries (%OE) and percentage of open arm time (%OT) (indices of anxiety). Data were analyzed using one-way ANOVA followed by Dunnett's test when appropriate. Results showed that both doses of 8-OH-DPAT decreased %OE (vehicle: 46.8±5.7; 8-OH-DPAT 5.6 nmol: 24.1±5.8; 10 nmol: 33.9±4.5) and %OT (vehicle: 31.50±6.3; 8-OH-DPAT 5.6 nmol: 12.2±3.0; 10 nmol: 12.8±3.0) but did not alter number of CE (vehicle: 7.5±1.0; 8-OH-DPAT 5.6 nmol: 7.1±1.3; 10 nmol: 8.8±0.9). Conclusion: The present study demonstrated that intra-VH infusion of 8-OH-DPAT produces a selective anxiogenic effect in mice. These results corroborate a previous study that demonstrated that the blockade of 5-HT1A receptors in the VH attenuates anxiety in the EPM (Brain Res., v.927, p.87-96, 2002). Financial Support: FAPESP, CNPq, Dept. Psychology/UFSCar.

74. BEHAVIORAL RESPONSES FOLLOWED BY CHEMICAL STIMULATION OF THE MIDBRAIN PERIAQUEDUCTAL GRAY IN MICE. Carvalho-Netto, E.F.; Nunes-de-Souza, R.L. Psychobiology, USP-RP; Pharmacology, FCF-Araraquara, UNESP, Brazil Objective: Ethopharmacological studies have suggested that mice are a more suitable species to study defensive reactions to proximal danger stimuli and their implications with the neurobiology of panic disorder. Studies with electrical and chemical stimulation (CS) of the dorsal periaqueductal gray (DPAG) have emphasized its involvement on panic disorder. We investigated the behavioral responses pattern followed by CS of the DPAG in mice. Method and Results: 5-6 days after cannula implantation in the DPAG, mice received intra-DPAG injections of saline (Sal) or D,L-Homocysteic acid (DLH) (1nmol or 5nmol in 0.05µl) over a period of 5s and were placed in a circular arena (floor divided in four equal quadrants), and their behaviors (number of crossings, jumps and rearing and time spent on freezing (s)) were recorded on videotape for 5 min. Results were analyzed at 30, 60, 120, 240 and 300s after injection procedure. DLH provoked a high number of jumps (Sal: 0.0±0.0; DLH 1nmol: 12.1±1.9; 5nmol: 14.3±1.9) and increased frequency of crossings (Sal: 9.3±1.3; DLH 1nmol: 41.4±7.2; 5nmol: 32.5±2.8) at the first interval of test. DLH also produced freezing (lower *F* value for all intervals $F_{2,32} = 3.89$, $p<0.05$) and decreased frequency of rearing (lower *F* value for all intervals, $F_{2,32} = 3.48$, $p<0.05$) from 60 to 300s. Conclusion: The present study demonstrated that mice exhibit a marked explosive motor behavior as an immediate response to the CS of the DPAG. Thus, we suggest the employment of this animal species to study the relationship between DPAG stimulation and panic disorder. Financial support: CAPES, FAPESP, CNPq

75. ACTIVE/PASSIVE AVOIDANCE IN THE MOUSE ELEVATED PLUS MAZE (EPM) AND OBSESSIVE COMPULSIVE DISORDER (OCD). Zhang, Z-J.; Dept. Psychiatry. Uniformed Services University of Health Sciences, Bethesda, MD 20814 USA; Schmid, S; Schmidt, D.E.; Salomon, R.M.; Hewlett, W.A. Depts. Psychiatry/Psychology. Vanderbilt University, Nashville, TN 37232 USA. Active and passive avoidance of uncertain risk exist in both OCD and the EPM. Change in risk-associated behavior occurs after 8-12 weeks SSRI treatment in both models. Since the 5-HT3 receptor antagonist, DAIZAC, selectively reduced passive avoidance in the EPM without affecting active avoidance, we examined changes in EPM avoidance behaviors associated fluoxetine treatment. ICR mice were treated with fluoxetine (10 mg/kg) for 12 weeks and tested in the EPM at weeks 2, 7 and 12. Changes in passive avoidance in the EPM occurred in a graded fashion over 12 weeks' fluoxetine treatment ($p<0.05$ @ 7 weeks; $p< 0.0001$ @ 12 weeks). Changes in active avoidance occurred only after 7 weeks treatment with fluoxetine (p=NS @ 7 weeks; $p<0.0001$ @ 12 weeks). Thus avoidance behaviors have independent time courses of change over 12 week's of fluoxetine treatment in the EPM. We also examined passive and active avoidance in 8 OCD patients treated with the 5-HT3 antagonist, ondansetron (6 mg). Passive avoidance was significantly reduced relative to active avoidance ($p < 0.01$), as seen with 5-HT3 antagonist treatment in the EPM. Results suggest that active and passive avoidance are independently regulated by different serotonergic treatments.

Human Disease Models

76. EARLY BEHAVIOURAL PHENOTYPES IN MOUSE MODELS OF HUNTINGTON'S DISEASE. Hickey, M.A.[1], Thomasian, S.[1], Gallant, K.[2], Levine, M.S.[2], Chesselet, M.-F.[1,3] [1]Depts Neurology and [3]Neurobiology and [2]Psychiatric and Biobehavioural Science, UCLA David Geffen School of Medicine, LA, CA, 90095 USA Huntington's disease (HD) is an incurable neurodegenerative disorder caused by an unstable elongated

polyglutamine tract in the huntingtin gene. Patients show cognitive, motor and emotional decline and knock-in and transgenic HD mouse models replicate many features of the disease. For drug trials, high-throughput behavioural screens with automated tests and clear, well-defined markers of disease progress are required. To this end, we now report reduced running wheel (RW) activity in the R6/2 transgenic mouse model of HD during the dark phase of the light cycle, from as early as 4.5 weeks of age. We also find reduced climbing behaviour at this age, when rotarod performance and grip strength are both normal. We have previously reported reduced climbing, increased anxiety and increased open field activity in the CAG140 knock-in mouse model of HD, at 1-1.5 months of age (Hickey et al., 2003; Menalled et al., 2003). We are currently investigating RW behaviour in this more subtle model of HD. These results show that behavioural deficits are present at very early ages in these mouse models. Additionally, these tests are ideal for use with large cohorts of animals for efficient, high-throughput drug screening. Hickey et al., Neurosci Absts 2003, 208.9, Menalled et al., J Comp Neurol, 465:11-26, 2003

77. EFFECTS OF L-TRYPTOPHAN DEPLETION AND LOADING ON RESPONSE DISINHIBITION IN HUMANS Jagar, AA; Dougherty, DM; Addicott, M; and Trotter, D Neurobehavioral Research Laboratory and Clinic University of Texas Houston Health Science Center. Serotonin function has been related to a variety of psychiatric syndromes (Bipolar Disorder, Depression) and even specific behaviors (impulsivity, aggression). Response disinhibition is one behavioral characteristic that may be involved in these conditions. In the laboratory, response disinhibition may be assessed through the use of a "go/no-go" task. In this task, participants identify matching numbers from a series of stimuli (5-digit numbers) that are presented rapidly (500 msec with 1500 msec between successive numbers). There are two types of matching trials: (1) “Go” trials where the participant is told to respond to a matching number that is black, and (2) “Stop” trials where the participant is told to withhold responding when the black matching number changes to red. This change from a black to a red matching number occurs at varying times (50, 150, 250 or 350 msec) after it first appears. The proportion of responses to the Stop trials is the primary measure of response disinhibition. In the present study, we investigated the effects of L-tryptophan depletion/loading procedures on response disinhibition; serotonin levels can be rapidly and acutely altered through the administration of amino acids given in proportions that either decrease (deplete) or increase (load) the availability of L-tryptophan (the precursor to serotonin). Three groups of men participated, and each group received one of three 50g amino acid mixtures: serotonin-loading (5.15 g L-tryptophan), serotonin-depleting (0.0 g L-tryptophan), or balanced (1.15 g L-tryptophan). The most important finding was the increase in response disinhibition among the L-tryptophan depleted group relative to the L-tryptophan loading and balanced groups.

78. THE BRATTLEBORO RAT AS A MODEL FOR ATTENTION DEFICIT-HYPERACTIVITY DISORDER. Danielson, JM; Schmitt, MP; Stevens, KE. Dept Psychiatry, University of Colorado Health Sciences Center; Denver CO 80262 and Medical Research Service, Dept of Veterans Affairs Medical Center, Denver CO 80220 USA Attention deficit-hyperactivity disorder (ADHD) effects both juveniles and adults. It is neither well understood nor well treated. There are many proposed models for ADHD; however, only one of these models accurately mimics naturally occurring developmental ADHD. With the exception of the male hyposexual rat model proposed by Kohlert and Bloch, other models require genetic manipulation, pharmacological, or surgical introductions in order to induce ADHD characteristics. We propose the Brattleboro rat (BB) [a naturally occurring mutant strain of Long Evans (LE)] as another model for ADHD. BB rats naturally exhibit characteristics of ADHD such as spontaneous hyperactivity and reduced behavioral inhibition. Preliminary data show that BB rats have a paradoxical response to stimulant treatment. When tested in an open-field maze, unmedicated BB rats travel a distance significantly greater than LE control rats. LE and BB showed divergent behaviors following a stimulant injection. LE rats traveled a greater distance while BB rats decreased their locomotor activity. These data suggest that the BB rat may be a useful model for studying ADHD.

79. OXYTOCIN REVERSES DECREASED SOCIAL INTERACTION IN TWO ANIMAL MODELS OF SCHIZOPHRENIA. Lee, P.R.[1]; Brady, D.[1]; Shapiro, R.A.[2]; Dorsa, D.M.[2]; Koenig, J.I.[1] [1]Maryland Psychiatric Research Center, Program in Neuroscience, University of Maryland Baltimore, Baltimore, MD 21228 USA; [2]Department of Physiology and Pharmacology, Oregon Health & Science University, Portland, OR 97201 USA. Exposure to stress during gestation and chronic administration of the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) have been proposed as animal models of schizophrenia. Both of these models are associated with pathological findings associated with schizophrenia including changes pre- and post-synaptic signaling molecules. Reduced social interaction, which may reflect aspects of the negative (deficit) symptoms, also have been found. Given the importance of oxytocin (OT) and vasopressin (VP) as mediators of social behaviors, we investigated whether prenatal stress and chronic PCP administration altered components of the brain OT or VP peptide systems. Sprague-Dawley rats (Charles River) were used in all studies. Prenatally stressed male rats were born to dams stressed using a repeated variable prenatal stress paradigm; they were evaluated and sacrificed as young adults. In the chronic PCP paradigm, young adult male were injected once daily with PCP (3 mg/kg) for two weeks; control rats received saline injections. Prior to sacrifice, social behavior was evaluated in all rats using the social interaction test. Chronic PCP-treated rats were tested 3 days after their final injection of PCP. *In*

situ hybridization histochemistry experiments using ^{35}S-labeled riboprobes for OT, VP, OTR, and V1aR mRNA and autoradiographic receptor ligand binding for OT and V1a receptors were performed on cryostat sectioned fresh frozen brain tissue. Prenatal stress and chronic PCP treatment were associated with diminished social interaction. Significant decreases in hypothalamic OT mRNA and changes in binding at amygdala OT and V1a receptors were noted in both experimental populations but not in appropriate controls. An acute, bilateral infusion of OT into the amygdala selectively restored normal levels of social interaction in animals from both models. These experiments may indicate that central OT is involved in the pathology of the negative symptoms of schizophrenia.

80. 5-HT1A RECEPTOR KNOCKOUT MICE EXHIBIT HYPERSENSITIVITY TO CORTICOTROPIN RELEASING FACTOR EFFECTS ON LOCOMOTOR BUT NOT ACOUSTIC STARTLE BEHAVIORS.Victoria Risbrough, René Hen, and Mark Geyer; Dept. of Neurosciences, UC San Diego, La Jolla CA; Center for Neurobiology & Behavior, Columbia University., NY, NY Constitutive loss of the serotonin (5-HT) 1A receptor results in increased behavioral avoidance of and autonomic responses to acute stressors in adult mice. Recent data indicate that the absence of 5-HT1A receptors during post-natal development only is sufficient to induce the increased anxiety-like phenotype exhibited by 5-HT1A receptor knockout (KO) mice. Hence, other systems involved in stress may be permanently altered by 5-HT1A receptor dysfunction during development. Recent data indicate that corticotropin releasing factor (CRF) receptors on serotonergic neurons in the dorsal raphe mediate both serotonergic transmission and behavioral responses during acute and chronic stress. Thus, the CRF system specifically may be altered in constitutive 5-HT1A receptor KO mice. To test this hypothesis, we compared the behavioral responses of 5-HT1A wild-type (WT) and KO mice to CRF. Behaviors tested were the defensive acoustic startle reflex (ASR) and locomotor activity. 5-HT1A WT and KO mice exhibited comparable increases in ASR and decreases in prepulse inhibition of startle after CRF (0.3 and 1 µg, 5 µl, ICV) treatment. 5-HT1A KO mice however exhibited significantly greater locomotor activation following CRF (0.5 µg, 5 µl, ICV) as compared to WTs, with CRF treatment increasing zone transitions in KO and WT mice 256% and 77% respectively above vehicle controls. Interestingly, acute blockade of 5-HT1A receptors in WT mice via administration of WAY 100,635 (1 mg/kg) had no effect on locomotor activity itself, yet blocked CRF induced increases in locomotor activity. These data support the hypothesis that 5-HT1A receptor deletion results in compensatory changes in the CRF system that are not reproducible with acute receptor deactivation, and indicate that these changes are specific to locomotor but not startle behaviors.

81. ORAL EFFICACY OF THE mGLU2/3 RECEPTOR AGONIST LY544344 IN ANIMAL MODELS OF PSYCHOSIS AND ANXIETY. McKinzie, D.L.; Knitowski K.M.; Hart, J.C.; Johnson, B.G.; Schoepp, D.D. Neuroscience Research Division, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285 Agonists at the mGlu2/3 receptor have been reported to be efficacious in animal models of psychosis and anxiety (Schoepp et al., 2003. Stress 6:189). To date, preclinical reports with mGlu2/3 agonists such as LY354740 have primarily utilized parenteral dosing due to low oral bioavailability. Recently, a peptidyl prodrug LY544344 (LY354740 N-2 alanine peptide) was synthesized. Following absorption from the gut, LY544344 is converted to the parent compound LY354740. LY544344 was tested for oral efficacy in reversal of phencyclidine-induced hyperlocomotor activity, mouse stress-induced hyperthermia and conditioned emotional responding (CER) in rats. The prodrug (LY544344) significantly reversed phencyclidine-induced hyperlocomotion following an oral dose of 30 mg/kg, whereas the parent compound (LY354740) was inactive at doses up to 100 mg/kg. In the mouse stress-induced hyperthermia assay, oral dosing of the prodrug significantly attenuated the stress response by over 30% following a minimal effective dose of 3 mg/kg. Conversely, a 30-mg/kg dose of the parent compound was necessary to produce a similar magnitude of hyperthermia reduction. In the CER assay, the prodrug significantly increased cue-suppressed responding at 10 and 30 mg/kg, indicating anxiolytic activity. Alterations upon baseline operant behavior were not observed at these doses. These data demonstrate that the prodrug LY544344 exhibits improved in vivo potency following oral administration and further confirms the utility of mGlu2/3 agonists in neuropsychiatric disorders.

82. MEDIATION OF STRESS-INDUCED HYPERTHERMIA IN THE MOUSE BY IONOTROPIC GLUTAMATE RECEPTOR LIGANDS. Rorick, L.M.; Hart, J.C.; McKinzie, D.L.; Neuroscience Discovery Research, Eli Lilly & Co., Indianapolis, IN 46285 USA. Similar physiological responses to stress exist between humans and many animal species. Consequently, assays such as stress-induced hyperthermia (SIH) have been used extensively in the search for novel anxiolytic drug targets and appear to have good predictive validity. Our laboratory has adapted the SIH procedure to measure stress induced by the fear of predation in mice. In this procedure, male DBA/2 mice were implanted with radio telemetric transmitters in the peritoneal cavity to measure baseline and stress-induced increases in body temperature following exposure to a novel cage containing soiled rat shavings. We have reported previously that several metabotropic glutamate receptor ligands effectively attenuated SIH in mice. To extend those results, the ability of various ionotropic glutamate receptor ligands to attenuate SIH was evaluated. The following compounds were tested: 1) the AMPA receptor antagonist GYKI-52466, 2) the AMPA receptor potentiator LY451646, 3) the glycine receptor partial agonist D-cycloserine, 4) the competitive

NMDA antagonist LY235959, 5) the iGlu5 kainate receptor antagonist LY382884, and 6) the glycine transporter (GlyT-1) inhibitors ALX-5407 and ORG24461-HCl. Results indicated that GYKI-52466, LY235959, and ALX-5407 significantly attenuated stress-induced hyperthermia in male DBA/2 mice. In contrast, LY451646, D-cycloserine, LY382884, and ORG24461-HCl did not significantly affect the SIH response. These results suggest that select ionotropic glutamate receptor ligands exhibit anxiolytic-like effects in this assay and may represent novel therapeutic targets for the treatment of stress- and anxiety-related disorders.

83. ANXIOUS BEHAVIOR IN MECP2 MUTANT MICE, A MODEL FOR RETT SYNDROME. Mwizerwa, O.; Berger-Sweeney, J. Dept. of Biology. Wellesley College, Wellesley, MA 02481 USA. Rett Syndrome (RTT) is a neurodevelopmental disorder that affects about 1 in 10,000 females. Studies have shown that about 80% of RTT cases have mutations in the X-linked methyl-CpG binding protein-2 (MeCP2) gene. Mice with deletion of Mecp2 have been developed as models of RTT. The onset of symptoms, such as loss of motor and cognitive abilities, occurs around 6 weeks of age in males, and later in females. The current study characterizes the emotional disturbances in mutant males at 5 weeks and in mutant females, who survive longer, at 3 - 9 months. Based on the human literature, we hypothesized that the mutants would display more anxious behavior and less exploratory behavior than wildtype mice. Four groups of mice were tested: wildtype males, null males, wildtype females and heterozygous females. A mouse was placed on the zero maze in white fluorescent light for 5 minutes, and the following measures were recorded: time in open and closed arms, freezing time, number of transitions and double transitions, number of head dips and rearings. At all ages, and in both sexes, the mutants exhibited more anxious behavior than wildtypes. At 5 weeks, null males spent a greater % of time in open arms, suggesting a desire to escape the maze, than wildtype males. At 3 and 6 months, heterozygous females spent a greater % of time in open arms and had greater double transitions between light and dark spaces. At 9 months, heterozygous females also had greater double transitions. However, there was no evidence of increased anxious behavior with increasing age. The data presented here support our hypothesis of increased anxiety-related behaviors in this RTT model, similar to reports in humans with Rett syndrome.

84. SYNAPTIC ALTERATIONS AND LOCOMOTOR IMPAIRMENTS IN AN MECP2-NULL MOUSE MODEL OF RETT SYNDROME. Storer, E.S.; Berger-Sweeney, J. Dept. Biology. Wellesley College, Wellesley, MA 02481 USA. Rett Syndrome (RTT) is a neurodevelopmental disorder that occurs in females, characterized by developmental arrest, mental retardation, and progressive motor dysfunction. About 80% of RTT cases are caused by mutations to the X-linked gene encoding methyl-CpG-binding protein 2 (MeCP2), a transcriptional repressor. Although the mechanism by which this mutation causes RTT is unclear, the mutated MeCP2 protein may cause a failure to repress genes controlling synaptic pruning during critical periods of synaptic plasticity. The resulting over-expression of synaptic pruning genes could cause a decrease in synaptic connectivity in the cerebral cortex, which may underlie the often severe cognitive and motor abnormalities associated with RTT. We have tested this theory using a mouse in which the Mecp2 gene is deleted. We measured synaptic density in somatosensory cortex of wildtype and Mecp2-null mice using synaptophysin immunohistochemistry and confocal microscopy. No significant differences were found in cortical synaptic density between mutant and wildtype mice. Synaptic density measurements were then correlated with performance on several behavioral tasks to determine whether there was an association between diminished cortical synapses and impaired motor and/or cognitive function. No correlation was found between cortical synaptic density and cognitive function, as measured by fear conditioning. However, a positive correlation existed between motor coordination, measured on the rotorod, and synaptic density in several regions of cortex. Our results suggest that lower synaptic density in somatosensory cortex is associated with impaired locomotor function, and suggest a link between MeCP2 and functional deficits in RTT.

Defense

85. PREDATOR ODORS AND THEIR AFFECTS ON OLFACTORY OSCILLATORY DYNAMICS. Catherine A. Lowry1 and Leslie M. Kay1,2. 1Committee on Neurobiology, 2Department of Psychology, University of Chicago, Chicago, IL 60637. Previous research has suggested that olfactory structures respond to predator odors with bursts of oscillatory activity in the beta frequency band (15-40Hz). However, those same oscillation bursts were seen in response to some non-predator odors. Additionally, one tested predator odor, trimethyl thiazoline (TMT), has recently been shown to elicit behavioral responses different from those to cat odors, thus evoking concerns that TMT is not perceived as a predator odor. We compare physiological and behavioral responses of TMT with six monomolecular odorants (toluene, amyl acetate, benzaldehyde, acetone, indole, vanillin) and with fox urine. Olfactory bulb (OB) local field potential (LFP) responses were recorded during five consecutive 2-minute presentations of odorants in a closed chamber, and behavior was recorded by webcam. Theta (3-15 Hz), beta (15-40Hz), low gamma (35-60Hz), and high gamma (60-115Hz) oscillation patterns are examined in response to each odor. We find similarities between predator and some non-predator odors across frequency bands and examine qualities of these odorants. We find differences across frequency bands between the two predator odors tested, supporting the idea that the perception of TMT, a synthetic component of fox feces, may deviate from the perception

of predator odors that could be encountered in the wild. Behavioral responses, such as freezing and attentive sniffing, are strongly correlated with concurrent oscillatory activity. Our results suggest that variations in oscillatory patterns can be attributed primarily to behavioral variations. Support: Brain Research Foundation Fay/Frank Seed Grant

86. BEHAVIORAL DIFFERENCES IN FOUR STRAINS OF MICE IN THE RAT EXPOSURE TEST (RET) Yang, M. 1; Augustsson, H. 2; Markham, C. 1; Blanchard, D.C. 1; Blanchard, R.J.1. 1 Pacific Biomedical Research Center, Univ of Hawaii 2 Unit for Comparative Physiology and Medicine, Swedish University of Agricultural Sciences. In order to facilitate behavioral, and potentially pharmacological, analyses of risk assessment behaviors in mice, a rat exposure test (RET) was devised and evaluated. This test provides a home chamber connected via a tunnel to a rat (predator) exposure area. Familiar substrate is provided to permit burying, and mouse subjects are habituated to the apparatus prior to exposure to an amphetamine-activated rat. When BALB/c, C57BL/6, CD-1, and Swiss-Webster mice were compared in this test, the two inbred strains (BALB/c and C57BL/6) tended to show more extreme values of particular defensive behaviors, compared to the two outbred strains (Swiss-Webster and CD-1). C57BL/6 mice showed more avoidance and higher levels of SAP, freezing, and burying than BALB/c and more than one or both outbred strains as well. BALB/c mice showed little defensive burying, in comparison to the 3 other strains. These findings are somewhat at variance with characterizations of anxiety in C57BL/6 and BALB/c mice, based on tests utilizing novel areas and noxious stimuli, suggesting strain differences in defensiveness to such stimuli, compared to antipredator defense levels. Nonetheless, with the exception of burying in BALB/c mice, all strains showed all defensive behaviors measured, to the rat stimulus. In particular, SAP levels were substantial in all strains tested, suggesting the usefulness of this test in assessment of the role of risk assessment in defense.

87. EFFECTS OF THE CRF ANTAGONIST SSR125543A ON AGGRESSIVE BEHAVIORS IN HAMSTERS. Catherine Farrokhi1, D. Caroline Blanchard2, Guy Griebel3, Mu Yang1, Chris Markham1, Robert J. Blanchard1. 1Department of Psychology, University of Hawaii, 2430 Campus Road, Honolulu, HI 96822, USA 2Pacific Biomedical Research Center, University of Hawaii, 1993 East West Road Honolulu, HI 96822, USA 3Sanofi-Synthelabo Recherche, Bagneax, France. Corticotrophin-releasing factor (CRF) and its receptor subtypes have been implicated in endocrine and behavioral responsivity to stress and emotion, including fear, anxiety, and aggression. SSR125543A is a new nonpeptide selective antagonist at the CRF1 receptor that has shown to produce an anxiolytic-like effect in a number of animal models of anxiety. The present study investigated effects of an oral dose of 0, 10, or 30 mg/kg of SSR125543A on aggressive behaviors of resident male Syrian hamsters toward male intruders. The high dose (30 mg/kg) of the CRF1 receptor antagonist produced a higher latency to bite and lower lateral attack frequencies and chase durations, indicating a reduction in aggression toward intruders in resident hamsters. The same dose of SSR125543A also enhanced frequency and duration of olfactory investigation, indicating that neither avoidance of the opponent nor deficiency in social activity is responsible for the reduction in aggression seen in these animals.

88. MODULATION OF PREDATORY ODOR PROCESSING FOLLOWING IBOTENIC ACID LESIONS TO THE DORSAL PREMAMMILLARY NUCLEUS. Markham, C.M.1,2 , Blanchard, R.J. 1, Cuyno, C.2, Canteras, N.S. 3, Blanchard, D.C.4 1 Depart of Psychol, Univ of Hawaii, 2 Haumana Biomedical Program, 3 Dept of Physiology and Biophysics, Univ of Sao Paulo, 4 Pacific Biomedical Research Center, Univ of Hawaii Previous studies have shown that electrolytic lesions of the dorsal premammillary nucleus (PMd) produce robust reductions in responsivity of rats to the presence of a live predator as well as to its odor, suggesting a critical role of the PMd in the modulation of defense. The present study investigated whether disruptions in defensive responding were specific to predators or if they may indicate a more general deficit in responding to pheromonal odors. Rats with ibotenic acid lesions of the PMd were exposed to the odor of a female rat in estrus as well as to the presence of a live cat and its odor. PMd lesions produced a dramatic reduction in freezing and avoidance to the cat odor and reductions in freezing, greater activity and enhanced risk assessment to cat exposure. However, PMd lesions produced no changes in response to the presentation of the female odorant. These results confirm earlier findings of attenuation in defensiveness following electrolytic PMd lesions while extending these findings to suggest that the reduced defensiveness occur specifically in response to predatory odors.

89. ASSOCIATIVE AND NONASSOCIATE RESPONSES TO FERRET ODOR EXPOSURE IN RATS. Masini, C.V.; Sauer, S.; Campeau, S. Dept. of Psychology and Center for Neuroscience. University of Colorado, Boulder, CO 80309 USA. In order to study brain processes involved in psychological stress, predators and their odors offer significant advantages over other models. To follow up on previous results whereby ACTH and corticosterone release were observed in response to ferret odors, behaviors of rats were assessed in a defensive withdrawal paradigm. After 4 days of acclimation to the behavioral apparatus, male Sprague-Dawley rats were exposed to either 5x5 cm towels with ferret odor (n = 16) or control / clean towel (n = 8) on day 1. On days 2 – 7, the same rats were exposed to control towels (conditioning and control-control groups / n's = 8) or ferret odor (habituation group / n = 8). On day 8, all groups were exposed to control towels. On day 1, rats exposed to ferret odor actively avoided the

ferret odor stimulus. Compared to control odor-exposed rats, ferret odor-exposed rats visited the stimulus less, spent less time in the area with the stimulus, and chewed less on the stimulus. On days 2 – 7, rats previously exposed to ferret odor that were exposed to the control odor exhibited behavior similar to the control-control group. On days 2 – 7 the rats undergoing repeated ferret odor presentation showed no behavioral habituation and avoided the towel stimulus. On day 8, the habituation group was exposed to the control odor and showed behaviors similar to control-control rats. These results suggest that behaviors induced by ferret odor do not habituate over several days, yet they also do not persist during extinction (i.e., no clear signs of conditioning).

90. HOW DOES FOX ODOR INFLUENCE THE BEHAVIOR OF NAIVE RATS? Endres, T.; Apfelbach, R.; Fendt, M. Dept. of Animal Physiology, University of Tübingen, Germany. In the past forty years, a lot of studies investigated the influence of predator odors on the behavior of naive rats. Most of these experiments were done with odor of cat fur/skin. One conspicuous behavior that can be observed during exposure to cat odor is freezing. Freezing is a prominent behavioral sign for anxiety and fear in rats. Recent studies showed that trimethylthiazoline (TMT, a component of fox feces) also can elicit freezing in naive rats (Vernet-Maury et al., 1984). In the present study, we showed the following behavioral effects of TMT in naive rats: I. TMT can be detected by rats up to a concentration of 2.5 x 10-9 % Vol. (olfactory threshold). II: The lowest TMT concentration which is able to initiate freezing behavior in naive rats is 1 x 10-3 % Vol. (behavioral threshold). III: There is no between-session habituation during daily TMT exposures over one week. IV: The acoustic startle response, which is potentiated by anxiety and fear, is increased during TMT exposure. V: TMT led to a long-lasting potentiation of the behavior in the elevated plus-maze, i.e. TMT-exposed rats show less open arm entries and a lower open arm ratio up to three days after TMT-exposure compared with control animals. Supported by the German Science Foundation (SFB550/C8).

91. THE NEURAL BASIS OF FOX ODOR-INDUCED FEAR BEHAVIOR. Fendt, M.; Endres, T.; Steiniger, B. Animal Physiology, University of Tübingen, Germany. Trimethylthiazoline (TMT), a component of the anal gland secretions of the red fox (Vulpes vulpes), is able to induce fear behavior (e.g. immobility) in naive rats. We think that TMT-induced immobility might be a useful animal model to investigate the behavioral, pharmacological, and neuroanatomical characteristics of unlearned fear. Here, we present first data to the neural basis of TMT-induced fear behavior.
Temporary inactivation of the bed nucleus of the stria terminalis (BNST) by local injections of the GABA agonist muscimol blocks TMT-induced immobility. This effect was also observed after inactivation of the medial parts of the amygdala but not after inactivation of the lateral and basolateral nuclei of the amygdala. First microdialysis studies to the neurochemical basis of TMT-induced fear showed that noradrenaline release within the BNST is increased during TMT exposure. Blockade of noradrenaline release by local microinjections of the alpha-2 receptor blocker clonidine into the BNST block TMT-induced immobility. Taken together, these results demonstrate that the BNST and its neurotransmitter noradrenaline are important parts of the neural pathway mediating TMT-induced fear behavior. The basolateral amygdala, which plays a crucial role in the learning of conditioned fear, is not important for TMT-induced fear, whereas the medial part of the amygdala which receives prominent olfactory input is involved. Supported by the German Science Foundation (SFB550/C8).

92. EFFECTS OF LESIONS TO THE DORSAL HIPPOCAMPUS ON DEFENSIVE BEHAVIORS. Pentkowski, N.1; Cuyno, C.2; Park, Y.1; Blanchard, R.J.1; and Blanchard, D.C.1,2 Dept. of Psychology 1, Haumana Biomedical Research Program 2, and Pacific Biomedical Research Center3. University of Hawaii, Honolulu, HI 96822 USA. Research has shown that the hippocampus may be involved in mediating unconditioned defensive behaviors upon exposure to a predatory stimulus. Furthermore, the dorsal hippocampus (DH) has been implicated in the acquisition, consolidation and retrieval of contextual representations by participating in the storage of the memory representation of the context. This study sought to investigate the role of the DH in unconditioned defensive behaviors as well as in the acquisition and consolidation of memories involving threat stimuli, by examining the effects of bilateral DH lesions on both unconditioned and conditioned defensive behaviors. Unconditioned defensive behaviors were assessed during exposure to three types of threat stimuli, cat odor, a live cat and footshock. The use of these three tests allowed for the comparison between painful and non-painful threat stimuli over a broad range of defensive behaviors, including risk assessment, avoidance and freezing. Conditioned defensive behaviors were assessed in the same context twenty-four hours after the threat exposure. DH lesions did not significantly alter unconditioned defensive behaviors during exposure to cat odor, a live cat, or footshock. In addition, DH lesions did not significantly modify conditioned defensive behaviors during cat odor exposure or footshock, but did increase locomotion during cat exposure. These results suggest that previous work implicating the hippocampus in unconditioned defensive behaviors to threat stimuli could be specific to the ventral hippocampus (VH). The finding that conditioned defensive behaviors to predatory threat stimuli are not DH dependent seems to fit with the two-process model of contextual fear conditioning.

Drugs and Development

93. BEHAVIORAL AND GROWTH EFFECTS INDUCED BY LOW DOSE METHAMPHETAMINE ADMINISTRATION DURING THE NEONATAL PERIOD IN RATS. Williams, M. T.,;Moran, M. S.; Vorhees , C. V. Cincinnati Children's Res Found. and Univ of Cinci College of Medicine, Cincinnati, OH 45229 USA. The investigation of methamphetamine exposure during neonatal development in rats has demonstrated that long-term spatial learning deficits are induced. A previous dose-response study showed that administration of 5 mg/kg methamphetamine, four times daily from postnatal day 11-20 produced these deficits, although the effects were not as severe as at higher doses of 10 or 15 mg/kg. This study examined concentrations of methamphetamine at or below 5 mg/kg given over the same period of time. Five different concentrations of methamphetamine (i.e., 5, 2.5, 1.25, 0.625, or 0) were administered every two hours four times daily from postnatal day 11-20. Body weights, zero maze performance, and Morris water maze learning were examined. A dose-dependent decrease in body weight was observed during the period of methamphetamine administration and these lower weights continued throughout adulthood for the 5, 2.5, and 1.25 mg/kg concentrations, although the adult decreases were negligible. No differences were noted in the Zero maze. In the Morris water maze during the acquisition period, dose-dependent differences in spatial orientation were seen, however non-dose related deficits were observed for other parameters. During the shifted platform phase ("reversal"), a similar dose-dependent difference in spatial orientation was observed, although no other effects were noted during this phase. Females performed worse than males regardless of treatment or the phase of learning in the Morris water maze. These data suggest that even lower doses of methamphetamine can alter learning and memory in adulthood, although with less consistent results than with doses higher than 5 mg/kg/dose. Furthermore, these data caution against using parameters in the Morris water maze that may make the task too difficult. Supported by NIH grants DA14269 & DA06733

94. CHANGES IN CORTICOSTERONE AND MONOAMINES FOLLOWING EXPOSURE TO METHAMPHETAMINE AND MDMA FOR 5 OR 10 DAY PERIODS IN THE DEVELOPING RAT Schaefer, T L; Able, J A; Skelton, M R; McCrea A E; Gudelsky; G A; Vorhees C V; Williams, M T Cincinnati Children's Res Found. and Univ of Cinci College of Medicine, Cincinnati, OH Administration of methamphetamine (MA) and methylenedioxymethamphetamine (MDMA) on P11-20 causes spatial learning deficits, and MDMA also causes sequential learning deficits, indicating unique effects of the drugs. We have found MA and MDMA to differentially affect corticosterone (CORT) and monoamine levels when administered on P11. To better characterize our multiple dose model, we investigated plasmatic CORT and monoamine levels in the striatum and hippocampus following extended MA and MDMA exposure periods. Pups were dosed with MA, MDMA, or SAL, 4 times a day, from either P11-15 (the critical period for MA) or from P11-20. Animals were killed either 18 hours following the last dose or on P30 to investigate potential long-term effects. CORT levels were significantly increased at 18 hrs. in the MA P11-15 animals. MA administration from P11-15 produced no significant change in striatal 5-HT, but MDMA exposure at this time caused a dramatic reduction when compared to SAL. An additional 5 days of MA, but not MDMA, produced an additive effect, causing a decrease in 5-HT. Unexpectedly, the P11-20 MDMA treated animals showed partial recovery from the 3 fold decrease in 5-HT observed in animals dosed from P11-15. No changes in dopamine were seen following any drug, even though it is known that a single day of MA exposure to an adult animal causes profound reductions in DA. No long lasting CORT or monoamine changes were observed on P30. These data further demonstrate the developmental differences between MA and MDMA exposure. Supported by NIH grants DA14269, DA06733

95. PROZAC EXPOSURE DURING NEONATAL DEVELOPMENT ALTERS THE SEXUAL DIFFERENTIATION OF BEHAVIOR. Fern¨¢ndez, M.1; Fortis, Y.1; Jorge, J.C.2 1 Department of Biology, R¨ªo Piedras Campus and 2 Department of Anatomy, Medical Sciences Campus, University of Puerto Rico, R¨ªo Piedras Campus, San Juan, P.R. 00931 Fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI), can also inhibit a key enzyme in the production of gonadal steroid neuroactive metabolites: 3-¦Á-hydroxysteroid oxidoreductase enzyme (3-¦Á-OH). We investigated whether chronic exposure to fluoxetine (10 mg/kg) during neonatal development (PN 1- PN 16) modulates neonatal and adult behaviors. In addition, we tested whether the sensitivity to diazepam is altered during adulthood. During neonatal development, odor-dependent behavioral tasks were performed. Adults were tested in the Elevated Plus Maze (EPM), Risk Assessment Behaviors (RAB¡¯s) over the EPM were also quantified. We found that prozac-exposed neonatal females took a longer time to find the surrogate dam ($p<0.05$) and spent more time with a surrogate dam instead of the natural dam than non-exposed neonatal females ($p>0.001$). In the EPM, prozac-exposed females were not responsive to the anxiolitic effects of Diazepam (DZP) as measured in the % time in the open arms and RAB's in the EPM. These effects did not correlate with total arm entries or total locomotor activity as measured directly in automated activity chambers. Overall, we found that females were more sensitive to prozac exposure diuring neonatal development than males. Support: NIMH-Hispanic COR (MH019134-15) to YF, NIH-COBRE I (RR15565), a Young Investigator Award (NIH-BRIN, RR16470), and the RCMI Program at MSC-UPR (G12RR03051) to JC Jorge.

96. THE EFFECTS OF IN-UTERO AND PRE-WEANLING EXPOSURE TO DEPLETED URANIUM ON NEUROBEHAVIORAL DEVELOPMENT OF THE RAT. Rossi III, J.; Bekkedal, M.; McInturf, S.; McDougle, F.; Lenger, A.; Allen, C.; Arfsten, D. Neurobehavioral Effects Laboratory - NHRC/EHEL, WPAFB, OH 45433 USA Four Hundred Eighty (480) male and female Sprague-Dawley rats, 8 weeks of age, were implanted in the leg gastocnemius muscle with either 0, 4, 8, 12, or 20 DU 1 x 2 mm pellets approximating 0.03%, 0.06%, 0.10%, and 0.15% by weight of a 500 g rat, or with control tantalum pellets, under isoflurane anesthesia. These animals (P1) were then cross-mated in various combinations at 30 days post-implantation. General reproductive toxicology screen measures which included; reproductive success, gestation weight gain, # of live-born pups (F1a generation), pup weight at Post Natal Day (PND), # of pups surviving to PND 4, and pup weight gain through PND 20 were acquired. In addition, neurobehavioral developmental measures from the Bowling Green/NEL neurodevelopmental battery were acquired including; maternal retrieval (PND 2), righting reflex (PND 4), ultrasonic vocalization index of separation distress (PND 7), rough and tumble play behavior (PND 24-27), open field behavior (PND 31-35), acoustic startle and pre pulse inhibition (PND 48-48), and water maze acquisition (PND 59-63). The P1 animals were again cross mated in equivalent combinations 120 days following their implantation (F1b generation). These animals were tested identically to the F1a rats. No reliable differences were found for either the general reproductive measures or the developmental neurobehavioral measures for the F1a rats (largest $F(8, 65) = 1.001$. $p > 0.40$). Initial evaluations of the F1b, and P1 animals suggest similar negative findings, although complete assessments have not been completed at the time of the writing of this abstract.

97. NEONATAL OXYTOCIN INCREASES ESTROGEN SENSITIVITY IN ADULT FEMALE RATS. Perry, A.N.; Cushing, B.S., Department of Psychiatry, University of Illinois at Chicago, Chicago, IL 60612 USA Oxytocin (OT) plays a major role in reproduction, especially in females, where OT stimulates uterine contractions, milk ejection, and sociosexual behavior. In adult female rats the effects of OT are short-term and estrogen-dependent. In contrast, during neonatal development OT appears to have long-term effects on the expression of sociosexual behavior. Neonatal manipulations of OT appear to have organizational effects on the expression of estrogen receptors in regions of the brain regulating female sexual behavior. These results suggest that neonatal OT may influence female reproduction by altering sensitivity to estrogen. We tested this prediction by treating neonatal females with OT and then subsequently determining the ability of estrogen to influence sociosexual behavior. On post-natal days 1-7, female Spraque-Dawley rats received one of 6 treatments, an intraperitoneal injection of one of three doses of OT, an OT antagonist, or saline vehicle. An additional group of animals was handled only. As adults, approximately 45 days of age, females were ovariectomized and given 14 days to recover, at which time they received a subcutaneous injection of one of three doses of estradiol benozate (EB) or oil for 7 consecutive days. Females then participated in a 30-minute paced sex test on the 3rd and 7th day of the injection regime. Low levels of EB stimulated significant levels of sexual activity only in females that were treated neonatally with OT. These findings support the hypothesis that neonatal manipulations of OT lead to increased sensitivity to estrogen in adulthood.

Cognition and Performance

98. FURTHER ANALYSYS OF FEMALE SEXUAL BEHAVIOR IN THE MULTIPLE PARTNER CHOICE TEST. *Ferreira-Nuño, A.; *Morales-Otal A.; °Paredes-Guerrero, R.; & *Velázquez-Moctezuma, J. *Área de Neurociencias. Instituto de Neurobiología. °Universidad Autónoma Metropolitana - Iztapalapa. When a female rat is tested in a UNAM, Juriquilla, Querétaro, México. situation in which she can control the sexual interaction she will move away from the male after each mount, intromission or ejaculation. This behavior has been called “pacing” and it is a crucial component for sex to be rewarding for a female rat. We have previously shown that when pacing was assessed in a condition where the female can choose among four sexually active males (the multiple partner choice test: MPCT) female sexual behavior display particular features, including a decrease in pacing behavior. Originally, the MPCT includes a security chamber surrounded by 4 cylinder with a sexually active male in each cylinder. The female can move freely between chambers but the males can’t follow her because the hole communicating with the security compartment is small for them to go trough. In the present study, females in natural estrous were tested in the MPCT in a condition where only one male was used and the remaining 3 cylinders were kept empty vs. 4 cylinders with a sexually active male in each chamber. Results showed that when only one male was present, females display higher levels of pacing. The percentage of exits after each mount, intromission or ejaculation was higher when the female was in contact with only one active male. The observed levels of pacing behavior were similar to those reported in previous studies where one male and one female are tested. In addition, females tested with only one male showed an increase of exploratory behaviour reflected by a higher number of entries into the empty chambers. Data suggest that the absence of other males facilitates the movement of the female across the different chambers and pacing can be displayed without limitations.

99. ILLUMINATION LEVELS IMPACT BEHAVIORAL PERFORMANCE IN AN OPEN FIELD OBJECT RECOGNITION TASK. Singletary, L.; Hohmann, C.F. Department of Biology. Morgan State University, Baltimore, MD 21251 USA. As nocturnal animals, mice normally display higher activity at night, during the scotophase. We hypothesize that illumination levels may impact behavioral performance by affecting levels of stress and anxiety in addition to activity. We here test if mice perform differently under red light, more closely resembling the nocturnal environment, then under, white light. The Open Field Object Recognition (OFOR) task, as performed by us, is a barometer for activity, anxiety and spatial learning, and easily can be done under different illumination conditions. Mice are first allowed to explore a three-foot diameter enclosure for assessment of overall activity (quadrant crossing) and anxiety (wall hugging vs. open space exploration). In subsequent trials, mice are allowed to explore five objects in this enclosure; an object is then rearranged to measure spatial learning; another object is later replaced by a new object to measure novelty response. 20 male and 20 female adult Balb/CbyJ mice were assigned to this task. Half of each sex was placed under red (darkroom) light and the others under fluorescent light. The animals' behavior was recorded on videotape and analyzed using Observer Video Pro II 4.0 software (Noldus), followed by statistical analysis (factorial Anovas, StatView). All mice showed significantly increased activity levels and reduced anxiety under red light but males were more substantially affected then females. This suggests that illumination during behavioral testing can impact behavioral outcomes in sex specific ways. Supported by: SO6-GM051971 and the National Association for Autism Research.

100. INFLUENCES OF MATERNAL EXPERIENCE ON COGNITIVE, EMOTIONAL, AND SOCIAL COMPETITION RESPONSES ACROSS THE LIFESPAN OF LONG-EVANS RATS. Love[1], G.; McNamara[2], I.; Kinsley[2], C.; Lambert[1], K. Dept. of Psychology, Randolph-Macon College, Ashland, VA 23116 USA[1]; Dept. of Psychology, University of Richmond, VA 23173 USA[2]. Prior research in our labs suggest that maternal rats exhibit cognitive advantages in the radial arm and dry land mazes (Kinsley et al., 1999) and reduced emotionality in the open field (Wartella et al., 2003). In the current study we investigated long-term effects of maternal experience on cognitive, emotional, and social competition responses [in the dry land maze (DLM), elevated plus maze (EPM), and a social competion task, respectively]in age-matched nulliparous (NULL; n=8), primiparous (PRIM; n=8), and multiparous (MULT; n=8) Long-Evans rats at 5 mo intervals across the lifespan. In the DLM, PRIM animals had faster latencies to the baited well on Day 2 of Phase II testing than NULL rats (at 10 mos of age); additionally, in the probe trials following each testing phase the PRIM rats exhibited faster latencies to the previously baited well than NULL animals across testing phases. In the EPM, PRIM and MULT animals exhibited longer durations in the open arms across testing phases. Social competition was assessed by introducing triads of weight-matched rats from all reproductive groups to the DLM task; at appx. 15 mos of age, the MULT rats retrieved the food reward on significantly more trials than the other groups. Thus, although all animals had weaned their litters by 4 mos of age, long-lasting effects on cognition, emotionality, and social competition persisted across the lifespan of these females. Currently, neuroanatomical data from the brain tissue of these females are being collected; preliminary results will be presented.

101. ACUTE EFFECTS OF SUCROSE AND NICOTINE ON COGNITIVE BEHAVIOR. D'Anci, K. E.; Schoemann, A. M.; Zablotsky, B.; Montalvan, C. R.; Taylor, H. A.; Kanarek, R. B. Psychology Dept. Tufts University, Medford, MA 02155 USA. Nicotine and sucrose independently and positively affect human cognition. Given the frequent concomitant use of nicotine and sweetened foods, the present study examined the combined effects of dietary sucrose and nicotine intake on cognition in college-aged smokers. Using a within subjects design, 13 participants refrained from smoking for 12 hours before consuming a beverage containing either sucrose (50 g) or aspartame. Fifteen minutes later, participants smoked a cigarette containing 1.1mg or 0.05 mg nicotine. Mood and craving questionnaires were given before consuming the beverage, before smoking, and after both the beverage and cigarette. Fifteen minutes after smoking, tasks measuring vigilance, mental rotation, spatial memory, and reading comprehension were administered. Craving and anger scores were significantly lower after participants smoked the high nicotine cigarette than after they had smoked the low nicotine cigarette. Reading comprehension was better following nicotine, independent of sucrose intake. Spatial memory was enhanced by sucrose alone, nicotine alone and both nicotine and sucrose. Nicotine reduced misses on the vigilance task, while sucrose alone and sucrose plus nicotine increased the false alarm rate on the task. Reaction time on the mental rotation task was lower in the sucrose alone or the nicotine alone conditions, but not when nicotine and sucrose were combined. Additionally, nicotine reduced errors in the mental rotation task. These findings suggest a complex relationship between nicotine and dietary sucrose on cognition.

102. SUGAR BINGEING ENHANCES DOPAMINE RELEASE IN THE ACCUMBENS, AND SHAM FEEDING ELIMINATES THE ACETYLCHOLINE SATIETY RESPONSE Avena, N.M.; Rada, P.; Hoebel, B.G. Department of Psychology. Princeton University, Princeton, NJ 08544. Repeated intermittent sugar intake in rats can lead to many behavioral and neurochemical signs of addiction. Most drugs of abuse increase dopamine (DA) in the nucleus accumbens (NAc), and do so every time as a pharmacological response. Palatable food also releases DA, but the effect wanes during a long meal and disappears with repetition. In Exp.1, rats (n=6/group) had a diet of 12–h

intermittent access to sugar and chow for 21 days while control rats only had access to sugar for 1 h during Day 1 and 21. Dopamine and acetylcholine (ACh) release was detected by microdialysis in the NAc shell. After three weeks, sugar intake in the bingeing rats increased extracellular DA to 130% of baseline, whereas animals without the repetitive bingeing experience show a blunted DA release. Extracellular ACh increased to 133% at the end of the sugar meal implicating ACh in satiety signaling. In Exp.2, rats on the same intermittent schedule ate with a gastric fistula open for the first h of access each day (sham-feeding), and DA was again released even on Day 21 (131%). As expected, rats that were sham-feeding consumed larger volumes of sugar than normal (55 ml vs. 18 ml), but in spite of this, ACh did not increase. These results suggest that the taste of sugar alone is sufficient to release DA in sugar-dependent animals. Thus, intermittent sugar binges release DA every time, analogous to a drug of abuse. The lack of ACh response during sham-feeding suggests that purging eliminates the ACh satiety signal. These findings may be related to the maintenance of excessive eating in bulimia nervosa.

103. LESIONS OF THE NUCLEUS ACCUMBENS DECREASE DISCOUNTING OF DELAYED BUT NOT PROBABILISTIC REWARDS. 1. Acheson, A .; 1. Farrar, A.; 1. Patak, M.; 1. Hausknecht, K.; 1. Kieres, A.; 3. de Wit, H; and 1 & 2. Richards, J. 1. Dept of Psychology, 2. Dept of Pediatrics, University at Buffalo, Buffalo, NY 14214. 3. Dept of Psychiatry, University of Chicago, Chicago, IL 60637 The effects of excitotoxic lesions of the nucleus accumbens (Acb) on discounting of reward value by delay and probability were tested. The delay discounting task measured how much delays to reward of 0, 1, 2, 4 and 8 s decreased the value of a water reward The probability discounting task measured how much probabilities of 1.0, 0.7, 0.4, 0.2, & 0.1 decreased the value of a water reward. Rats were trained on the delay discounting (n=24) and probability discounting (n=24) tasks prior to surgery. The delay and probability groups were than given 0.15 M quinolinic acid (n=12) or sham (n=12) lesions aimed at the Acb (AP +1.6, ML ±1.5, DV -7.1.). Following recovery from surgery, delay and probability discount curves were obtained. In general increasing the delay to reward or decreasing the probability of reward systematically decreased the value of the reward. Rats in the Acb lesion group discounted the value of delayed rewards less than rats with sham lesions. In contrast, rats in the Acb lesion group tended to discount the value probabilistic rewards more than rats with sham lesions. These results indicate that Acb lesions have differential effects on discounting of reward value by delay and probability. A previous study using a different behavioral task reported that Acb core lesions increase delay discounting (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001). This result in conjunction with the pattern of results obtained from the current study indicates that Acb lesions may not directly effect delay discounting. The changes in discounting observed in Acb lesioned rats may be the consequence of learning and/or memory impairments that decrease the rats' ability to adapt to rapid changes in the delay to reward. The absence of a similar effect on probability discounting indicates that these impairments are specific to delay.

Saturday, June 19:

8:30-10:30 Symposium 4: From complex phenotypes to genes: Finding the links in dependence and emotionality

MICROARRAY ANALYSIS IDENTIFIES CANDIDATE GENES AND SIGNALING PATHWAYS FOR ACUTE FUNCTIONAL ETHANOL TOLERANCE. Hoffman, P.L.; Bhave, S.V.; Hudson, H.R.; Tabakoff, B. University of Colorado Health Sciences Center, Denver, CO 80262 Acute functional tolerance (AFT) to ethanol develops during a single exposure to ethanol, and may be a predisposing factor for the development of ethanol dependence. Genetic factors influence AFT, as evidenced by the selective breeding of lines of mice that display high (HAFT mice) or low (LAFT mice) AFT to the incoordinating effect of ethanol measured on a stationary dowel. We combined selective breeding, which segregates genes contributing to the phenotype of AFT, quantitative trait locus (QTL) analysis, which identifies regions of the mouse genome that affect AFT, and DNA microarray analysis, which determines differentially expressed genes in the brains of HAFT and LAFT mice, to identify candidate genes that contribute to AFT. RNA from whole brain of mice from two replicate lines of HAFT and LAFT mice was analyzed with Affymetrix MGU74A gene arrays, and mapping the differentially expressed genes (determined by two statistical analyses) to QTLs for AFT provided evidence for a signaling pathway involving NMDA receptor activity, phosphorylation and cellular localization as a possible mediator of AFT. We confirmed our results using the Affymetrix MOE430A array, which contains 10,000 more probes, in a later generation of HAFT and LAFT mice, and also identified previously unrepresented genes involved in receptor phosphorylation and endocytosis that may contribute to the proposed signaling cascade for AFT. We are currently using microarray analysis to identify differentially expressed genes in brains of transgenic and knockout mice that display differences from wild-type mice in other alcohol-related behaviors. Supported by NIAAA and the Banbury Fund.

COMPLEMENTARY APPROACHES IDENTIFY THE CANDIDATE GENE ALPHA-SYNUCLEIN FOR ALCOHOL PREFERENCE IN ALCOHOL- PREFERRING AND ALCOHOL-NONPREFERRING RATS. L. G. Carr. Indiana University School of Medicine, Indianapolis, IN 46202. Alcoholism is a complex disorder that is influenced by multiple genes (quantitative trait loci, QTLs), the environment, and their interactions. To simplify the genetic and phenotypic complexity of the alcoholic phenotype, alcohol-preferring (P) and -nonpreferring (NP) rats were developed on the basis of alcohol preference and consumption as an animal model of alcoholism. Complementary with QTL analysis, total gene expression analysis (TOGA) was utilized to identify genes that are differentially expressed in discrete brain regions between the alcohol-naïve, inbred alcohol-preferring (iP) and -nonpreferring (iNP) rats. Alpha-synuclein, expressed at greater than 2-fold higher levels in the hippocampus of the iP than the iNP rat, was prioritized for further study. Similar to alpha-synuclein mRNA levels, protein levels in the hippocampus and caudate putamen were higher in iP rats than iNP rats. Sequence analysis identified two single nucleotide polymorphisms in the 3'-untranslated region (UTR) of the cDNA and five polymorphisms in the promoter. The polymorphism was employed to map the gene, using recombination-based methods, to chromosome 4 within a highly significant QTL with a maximum lod score of 9.2. A nucleotide exchange in the iNP 3'-UTR reduced expression of the luciferase reporter gene in SK-N-SH neuroblastoma cells. Combining selective breeding, QTL and TOGA analysis generated a specific gene of interest, alpha-synuclein, from a broad QTL region and a multitude of differentially expressed genes. (AA07611, AA10707)

THE INVOLVEMENT OF PER GENES IN COCAINE AND ALCOHOL ADDICTION Rainer Spanagel Dept. of Psychopharmacology, CIMH Mannheim, Germany In recent years enough evidence has accumulated to suggest that circadian rhythms might be involved in addictive behaviour. Circadian fluctuations have been observed in behavioural and pharmacological effects of drugs of abuse such as cocaine or alcohol. Using Per mutant mice we showed for the first time in mammals that Per1 and Per2 genes, two important molecular components of our internal clock modulate cocaine and alcohol-induced behaviour. Per2 mutant mice exhibit an increased cocaine-induced sensitisation and correspondingly an increase in cocaine reward compared to wild-type (wt) mice. In contrast, Per1 mutant mice exhibit no cocaine sensitisation and a clear decrease in cocaine reward. Using in vitro binding assays and in vivo challenge studies with selective agonists we have now evidence for the potential involvement of dopamine receptors in cocaine–induced sensitisation in Per mutant mice. Thus dopamine D1 receptors appear to play a critical role in the opposing responses of Per1 and Per2 mutant mice following repeated cocaine administration. In summary these results show the importance of Per genes in processes related to addiction and the possible involvement of dopamine D1 receptors causing opposite responses in Per1 and Per2 mutants.

FUNCTIONAL NEUROANATOMY AND GENETICS OF TRAIT ANXIETY: CENTRAL ROLE FOR THE DORSOMEDIAL PREFRONTAL CORTEX. Heilig, M. (1); Sommer, W. (1); Arlinde, C. (1); Kalisch, R (2).; Auer, D.P (2).; Landgraf, R. (2): 1: Div of Psychiatry, NEUROTEC, Karolinska Inst, Stockholm, SWEDEN; and 2: Max Planck Inst for Psychiatry, Munich, Germany. The neural basis of trait anxiety is poorly understood. Behavioral differences are presumably encoded by stable patterns of differential gene expression in key brain areas, but neither the anatomical nor molecular substrates are presently known. We addressed this issue using rats bred for high (HAB) and low (LAB) anxiety-related behavior, resp., which also differ in their behavioral response to the anxiolytic diazepam. Using high-field pharmacologic fMRI (phMRI), we identified the dorsomedial prefrontal cortex (dmPFC) as a brain area with differential neuronal response to diazepam, making this region a candidate for mediating trait anxiety. Guided by these data, we performed regional DNA microarray analysis, revealing a relative up-regulation of a cAMP-specific phosphodiesterase (PDE4B) gene in the dmPFC of HABs. Supporting the functional relevance of this finding, rolipram, a non-selective PDE-inhibitor, modulated anxiety-related behavior. We propose that high trait anxiety is related to impaired inhibitory control by the dmPFC over lower anxiety centers and that this is linked to regional hypofunction of the cAMP second-messenger system.

10:45-11:45 Keynote Speaker: George Koob

THE DARK SIDE OF ADDICTION: NEUROPHARMACOLOGICAL DISRUPTION OF THE BRAIN REWARD AND STRESS SYSTEMS. Koob, G. Dept. of Neuropharmacology, The Scripps Research Institute, La Jolla, CA 92037 USA. Drug addiction is a chronic relapsing disorder characterized by compulsive drug intake, loss of control over intake, and impairment in social and occupational function. Animal models have been developed for various stages of the addiction cycle, with a focus in our work on the motivational effects of drug dependence. A conceptual framework focused on allostatic changes in reward function that lead to excessive drug intake provides a heuristic framework with which to identify the neurobiologic mechanisms involved in the development of drug addiction. Neuropharmacologic studies in animal models have provided evidence for the dysregulation of specific neurochemical mechanisms in specific brain reward and stress circuits that provide the negative motivational state that drives addiction. These include dysregulation of specific neurochemical mechanisms not only in specific brain reward systems in the extended amygdala (opioid peptides, gamma-aminobutyric acid, glutamate and dopamine), but also is recruitment of brain stress systems (corticotropin-releasing factor and norepinephrine) and dysregulation

of brain anti-stress systems (neuropeptide Y). The allostatic model not only integrates molecular, cellular and circuitry neuroadaptations in brain motivational systems produced by chronic drug ingestion with genetic vulnerability, but also provides the key to translating advances in animal studies to the human condition.

3:30-4:45 Oral Session 2: Chemistry and Behavior

A MEDIAL AMYGDALOID - VENTROMEDIAL HYPOTHALAMIC PATHWAY FOR FEEDING BEHAVIOR. Grundmann, S.; Pankey, E.; Cook, M.; Wood, A.; Rollins, B.; King, B. Department of Psychology, University of New Orleans, New Orleans, LA 70148. Previous research has shown that bilateral lesions of the most posterodorsal aspects of the medial amygdala, or bilateral knife cuts of the stria terminalis just as it exits the amygdala, result in hyperphagia and obesity in female rats. Examination of anterograde degeneration by the cupric silver method in rats with unilateral posterodorsal amygdaloid lesions revealed a dense pattern of degenerating terminals in the ipsilateral ventromedial hypothalamic nucleus, but not the contralateral nucleus. In the present study, female rats with unilateral ventromedial hypothalamic lesions were given unilateral posterodorsal amygdaloid lesions 20 days apart. Unilateral ventromedial hypothalamic lesions resulted in hyperphagia and excessive weight gains. Unilateral amygdaloid lesions that were contralateral to the ventromedial hypothalamic lesions resulted in additional hyperphagia and excessive weight gains compared to operated control animals, but amygdaloid lesions ipsilateral to the ventromedial hypothalamic lesions did not. It was concluded that the effects of the two lesions are not additive, and that the medial amygdala and ventromedial hypothalamus are part of the same pathway regulating feeding behavior and body weight regulation.

ASSESSMENT OF THE POTENTIAL APPETITE SUPPRESSANT EFFECTS OF CANNABINOID CB1 ANTAGONISTS IN RATS. McLaughlin, P.J.; Swezey, L.; Winston, K.; Thotapally, R.; Liu, Q.; Makriyannis, A.; Salamone, J.D. Dept. of Psychology and School of Pharmacy, Storrs, CT, USA, 06269-1020. Cannabinoid agonists and antagonists have been suggested as potential treatments for a variety of different conditions. It has been reported that acute administration of CB1 antagonists reduces food intake in rats, and based upon these observations it has been suggested that CB1 antagonists could be useful as appetite suppressant drugs. The present studies were conducted to study the effects of several CB1 antagonists on food intake across a broad range of paradigms. Blockade of CB1 receptors reduced food reinforced lever pressing on both fixed ratio 1 and fixed ratio 5 schedules. The time course of this effect varied markedly across different drugs, with half-lives ranging from 4-22 hrs. Several CB1 antagonists also were tested on procedures involving direct measurements of food intake. In some studies, foods with different macronutrient composition (high-fat vs. high-carbohydrate vs. lab chow) were employed. Across a number of different CB1 antagonists, intake of all three food types was significantly reduced in a dose-related manner. These findings support the hypothesis that CB1 antagonists could be useful for the suppression of appetite, although further research must focus on the extent to which other behavioral effects (i.e., motor impairments, food aversions) contribute to the drug-induced suppression of food intake. Moreover, additional research must focus upon the extent to which the reduction of food intake induced by the current generation of drugs is dependent upon blockade of CB1 receptors or upon inverse agonist activity.

MODULATION OF ORAL WOUND HEALING: A ROLE FOR HPA ACTIVITY. Engeland, C.G. [1]; Cacioppo, J.T. [2]; Marucha, P.T. [1]. [1]Dept. of Periodontics. University of Illinois at Chicago, Chicago, IL 60612 USA; [2]Dept. of Psychology. University of Chicago, Chicago, IL 60637 USA. Both aging and psychological stress are known to alter numerous immune components including inflammation, and stress has been shown to delay wound healing. However, whether such effects are sexually differentiated is largely unknown. To determine the effects of gender and age on wound healing, a 3.5 mm round wound was placed under local anesthesia on the hard palates of 120 younger (18-35 years) and 92 older (50+ years) male and female volunteers. Immediately prior to the wounding process and 15, 30 and 60 min afterward, blood was drawn from which ACTH and cortisol levels were determined. Wounds were videographed and measured daily until healed. Analyses revealed that older individuals healed 19.5% slower than younger individuals ($P<.001$) regardless of gender, and women healed 18.6% slower than men ($P<.01$) regardless of age. Given that basal cortisol levels were lower in the older group ($P<.05$) and basal ACTH levels were lower in women ($P<.01$), these delays in wound healing may have stemmed from differences in baseline HPA activity. Furthermore, faster healing times were related to higher baseline levels of ACTH in men ($P<.01$) and cortisol in women ($P<.01$). In addition, pain expectation (i.e., anticipatory stress) was predictive of wound sizes, such that individuals who expected higher pain from wounding exhibited smaller sized wounds ($P<.01$). Higher pain expectation was also related to reduced mRNA expression for pro-inflammatory cytokines ($P<.001$). Thus, higher levels of stress hormones at the time of wounding were associated with smaller subsequent wound sizes and shorter healing times in both sexes, possibly due to the anti-inflammatory properties of cortisol. (Supported by NIH P01AG16321)

MDMA ('ECSTASY') AND METHAMPHETAMINE COMBINED: MORE TOXIC THAN EITHER DRUG ALONE? McGREGOR, I.; CLEMENS, K.; VAN NIEUWENHUYZEN, P.; LI, K.; HUNT, G.; CORNISH, J. School of Psychology, University of Sydney, Australia MDMA ("Ecstasy") and Methamphetamine ("Speed", "Ice", "Meth") are illicit drugs that are increasingly used in combination. This happens both deliberately in polydrug users or inadvertently when users consume pills that contain both MDMA and METH. The effects of MDMA/METH combinations are largely uncharacterised and in a series of studies we have recently investigated this. Typical administration involved giving rats 4 injections, one every 2 h, of equivalent doses of MDMA, METH or MDMA/METH cocktail at an ambient temperature of 28? C. Body temperature, locomotor activity and head-weaving were assessed during acute drug administration while social interaction and neurochemical parameters were assessed 4-7 weeks later. Acutely, MDMA, METH and MDMA/METH all increased locomotor activity, while pronounced head-weaving was seen only with MDMA/METH and METH treatment. Acute hyperthermia appeared greatest with MDMA/METH combinations and but was also seen with MDMA alone. Several weeks after drug administration, MDMA, METH and MDMA/METH treated rats showed decreased social interaction relative to controls. MDMA treatment caused 5-HT and 5-HIAA depletion in several brain regions, while METH treatment reduced dopamine in the prefrontal cortex. Combined MDMA/METH treatment caused 5-HT and 5-HIAA depletion in several brain regions and a depletion of dopamine and DOPAC in the striatum. The long-term neurochemical depletion seen with MDMA/METH appeared similar regardless of whether the two drugs were given as a cocktail or given in doses separated by 4 hours. Taken together these data suggest that MDMA/METH combinations may be particularly hazardous in terms of acute hyperthermia and long-term neurotoxicity.

THE EFFECT OF ENJOYMENT ON PERCEIVED DURATION: DOES WHAT YOU WATCH FIRST INFLUENCE WHAT YOU WATCH SECOND? Wojtaszczyk, J.A. & Carpenter, D.L. Department of Psychology, Saint Bonaventure University, Olean, NY 14778. Time perception is a phenomenon that humans encounter daily. Research indicates that when presented with an enjoyable stimulus, humans perceive time to be shorter than when they encounter a non-enjoyable stimulus. The base time hypothesis indicates that the first stimulus perceived should always receive the same time estimation. The hypothesis of this study is when two stimuli with the same enjoyability, there should be no difference in time estimation, whether it is two enjoyable movies shown concurrently or two non-enjoyable movies. When an enjoyable stimulus is followed by a non-enjoyable one, time estimation should increase. When a non-enjoyable stimulus is followed by an enjoyable one, time estimation should decrease. There should be no difference in time estimation for any of the initial stimuli, verifying the base time theory. Participants viewed two movies and were asked to estimate time and rank enjoyability. ANOVA results indicate no significant difference in any of the variables, therefore not supporting the hypothesis. t tests done between groups receiving two of the same stimuli showed no significance, supporting the hypothesis. t tests between base time scores showed no difference, therefore supporting hypothesis. The concept of an internal clock is something that has been accepted, and neurological models have arisen for three basic components: the clock, the reference memory and the decision-making component. The basal ganglia have been implicated as a primary contender for timing within the brain. Dopamine may play a crucial role in the estimation of duration. Evidence has shown that an increase in dopamine decreases time perception and a decrease leads to increased time perception. The current study suggests elaboration of these models is needed.

Sunday, June 20:

8:30-10:30 Symposium 5: Introduction to behavioral measures of impulsivity for neuroscience

METHODOLOGIES AND PROCEDURES USED FOR THE LABORATORY BEHAVIORAL ASSESSMENT OF IMPULSIVITY. Dougherty, D.M. Department of Psychiatry and Behavioral Sciences. The University of Texas Health Science Center at Houston, TX 77030 USA. Impulsivity is a complex construct that has been defined and measured in various ways. This presentation provides an overview of major theoretical aspects of impulsivity and an introduction to their assessment. This overview will include discussion of methodological issues and how the various domains of assessment operationalize impulsive responding. The introduction to assessment will include descriptions of several laboratory behavioral measures that are sensitive to both trait- and state-dependent aspects of impulsivity. Discussion of the relevance of these modes of assessment to the behavioral neurosciences will follow.

ASSESSMENT OF STATE-DEPENDENT MODIFICATION OF IMPULSIVITY, Marsh, D.M. Department of Psychiatry and Behavioral Sciences. The University of Texas Health Science Center at Houston, TX 77030 USA. This presentation provides some specific examples of impulsivity assessment from the state-dependent perspective. According to this perspective, transient fluctuations in impulsivity may occur as the result of internal (e.g., psychiatric disorder) or external (e.g., pharmacological treatment) events. A number of different laboratory

behavioral procedures have been developed that are sensitive to these state-dependent aspects of impulsivity. This presentation describes the use of one of these measures, the Immediate and Delayed Memory Tasks, to explore changes in impulsivity as a result of alteration of serotonin function and administration of alcohol. There is initial experimental evidence indicating that baseline plasma L-tryptophan levels (a peripheral marker of central serotonin function) can modify the behavioral effects of alcohol. In this portion of the symposium, a study is described that examined the behavioral effects of alcohol (0.65 g/kg) consumption following either an L-tryptophan depletion or loading amino acid drink on impulsive responding. The most significant finding was a significant interaction, with alcohol consumed after L-tryptophan depletion producing a disproportionate increase in impulsivity compared to control conditions (e.g., alcohol consumed after L-tryptophan loading). This study is important because it: (a) demonstrates that the biological state (low serotonin function) appears to determine the behavioral effects of alcohol; and (b) provides a model of how laboratory measures may be integrated into behavioral neuroscientific studies.

ASSESSMENT OF TRAIT-DEPENDENT ASPECTS OF BEHAVIORAL IMPULSIVITY Mathias, C.W. Department of Psychiatry and Behavioral Sciences. The University of Texas Health Science Center at Houston, TX 77030 USA. There is a growing body of evidence indicating that impulsivity is an important factor related both to distinct neurobiological differences, and to differential response to treatment. Some researchers have proposed that impulsivity is an underlying factor in a number of psychiatric diagnoses and could be one element accounting for heterogeneity within diagnostic categories. This presentation provides an overview of how different approaches to impulsivity assessment can be applied from a trait-dependent perspective. This perspective involves assessing relatively stable differences in impulsive responding between groups who may be experiencing psychiatric disorder or who exhibit other at-risk behaviors. This laboratory behavioral evidence may be useful for bridging the gap between traditional neuroscientific evidence and more complex behavior syndromes.

TRAIT AND STATE IMPULSIVITY IN BIPOLAR DISORDER Swann, A.C. Vice-Chair of Research, Department of Psychiatry and Behavioral Sciences. The University of Texas Health Science Center at Houston, TX 77030 USA. Impulsivity is a fundamental component of a number of psychiatric conditions including Bipolar Disorder. Bipolar Disorder, however, is a complex psychiatric condition composed of phases of illness. These phases can include episodes of mania or depression as well as inter-episode periods during which symptoms are not evident. Different aspects of impulsivity may be more relevant during different phases of illness than others. This presentation will explore the clinical course of Bipolar Disorder and its relationship to different aspects of impulsivity. Specifically, state- and trait-dependent aspects of impulsivity will be compared across phase of illness in Bipolar Disorder. State-dependent aspects of impulsivity are, in this case, impulsive behaviors that fluctuate due to the influence of internal processes (i.e., Bipolar Disorder phase). Trait-dependent aspects of impulsivity are patterns of impulsive responding that remain stable across different internal or environmental conditions. This presentation serves as an example of how consideration of measurement techniques for assessing impulsivity is relevant to the application of behavioral neuroscience in addressing diagnostic and treatment issues relevant to psychiatric conditions.

10:45-12:15 Oral Session 3: Development, Differences & Disease Models

INNATE BRAIN DIFFERENCES UNDERLYING THE VULNERABILITY TO DEPRESSION. Shumake, J. ; Gonzalez-Pardo, H. ; Conejo-Jimenez, N. M. ; Gonzalez-Lima, F. Dept. of Psychology, University of Texas at Austin, Austin, TX 78712, USA; Dept. of Psychology, University of Oviedo, Oviedo, Asturias, Spain. The goal was to map inborn brain differences underlying the predisposition to helpless behavior and depression in congenitally helpless rats, a genetically selected strain predisposed to show depressive behavior. There are a number of brain regions showing abnormal metabolism in the naïve congenitally helpless rats when they become adults (Shumake and Gonzalez-Lima, 2003). Some of these alterations may be innate while others may be due to environmental factors, such as maternal care and postnatal stress. To identify which brain structures show innate differences, the brains of newborn rats from congenitally helpless and non-helpless strains were compared using cytochrome oxidase histochemistry, an endogenous marker of regional metabolic capacity. A smaller subset of the regions affected in adults showed significant ($p<0.01$) hypometabolism in the newborn brains, including paraventricular and anterior hypothalamus, habenula, hippocampal CA1, CA3 and subiculum, lateral septal nucleus, anterior cingulate cortex, and bed nucleus of the stria terminalis. The brain metabolic pattern in the newborn rats suggests that their helplessness vulnerability is linked to altered metabolism in limbic and hypothalamic regions that are the key for controlling the HPA axis that regulates the stress response. This implies that vulnerable animals have innate deficits in the brain systems that would allow them to cope with stress, predisposing them in this manner to more readily develop helpless and depressive behaviors. Supported by NIH grant R01 NS37755.

SOCIAL WITHDRAWAL, NEOFOBIA, AND STEREOTYPED BEHAVIOR IN DEVELOPING RATS EXPOSED TO NEONATAL ASPHYXIA. Laviola G, Adriani W, Rea M, Aloe L (*), Alleva E. Sect. Behavioral Neuroscience, Dept. Cell Biology & Neuroscience, Istituto Superiore di Sanita', Roma, and (*) Institute of Neurobiology & Molecular Medicine, CNR, Roma, Italy Perinatal asphyxia is a concern for public health and may

promote subtle neuropsychiatric disorders. Anoxic insults to neonatal rats cause long-lasting neurobehavioral deficits. In the present study, we focussed on changes in emotional behaviors as a consequence of neonatal asphyxia in Wistar rats. Newborn pups (12-24 h after birth) underwent a single 30-min exposure to a 100% N2 atmosphere (or air). The offspring was tested for a) locomotor and exploratory activity with or without a d-amphetamine challenge (0, 1, or 2 mg/kg) on pnd 15; b) social interactions and novelty seeking during adolescence; c) levels of the brain-derived neurotrophic factor (BDNF). In the open-field test (pnd 15), N2-exposed pups injected with the high (2 mg/kg) amphetamine dose exhibited reduced levels of locomotor hyperactivity, and a more marked involvement in stereotyped behaviors. Individual differences emerged in the locomotor response to the novelty-seeking test: two subgroups of rats (separated on the basis of the median value) showed either arousal/attraction or avoidance/inhibition in response to free-choice novelty. The N2-exposed group showed a more marked novelty-induced avoidance and inhibition. Time devoted to allogrooming and play-soliciting behaviors was reduced, whereas object exploration was increased. Levels of BDNF were reduced in the striatum of N2-exposed rats, suggesting poorer synaptic performance of dopamine pathways. In conclusion, these findings suggest an increased risk of developing social withdrawal, neophobia and behavioral stereotypies (common symptoms found in schizophrenia and autism) as a consequence of neonatal asphyxia in preterm humans.

ACETYLCHOLINE AND ITS RELATED mRNAs EXPRESSION BY HIGH ACETALDEHYDE IN THE RAT FRONTAL CORTEX. Jamal, M.; Ameno S; Ameno, K.; Kumihashi, M.; Wang, W.; Uekita, I.; Kubota, T.; Ijiri, I. Dept. of Forensic Medicine, Faculty of Medicine, Kagawa University, Ikenobe, Miki, Kagawa 761-0793, Japan. Acetaldehyde (AcH) is a highly toxic compound, and its high concentration can induce central nervious system depression and produce some toxic effects. These effects are far more commonly found in Asians and some American Indians due to the deficient activity of aldehyde dehydrogenase 2 in these groups. Here we examined the effect of high AcH on in vivo acetylcholine (ACh) release and mRNAs levels of choline acetyltransferase (ChAT), acetylcholinesterase (AChE), choline transporter (CHT) and vesicular acetylcholine transporter (VAChT) in the rat frontal cortex. ACh release was determined by in vivo brain microdialysis coupled with a HPLC-ECD technique. The messenger RNA levels were analyzed by a reverse transcription (RT) coupled to complementary DNA (cDNA) amplification using a polymerase chain reaction (PCR) technique. Rats were treated with cyanamide (CY, 50 mg/kg) and 60 min later with ethanol (EtOH, 2g/kg) intraperitoneally. A significant decrease in ACh release was observed in the dialysate at 240 min after EtOH administration in the CY+EtOH groups than in the EtOH groups. RT-PCR analysis showed a remarkable decrease of CHT and VAChT mRNAs levels at 240 min after EtOH injection in the CY+EtOH groups than in the EtOH groups. ChAT and AChE mRNAs levels did not change significantly in either the CY+EtOH groups or the EtOH groups. The findings suggest that decreased expression of mRNAs levels of CHT and VAChT are likely consequence of high AcH leading to the decrease of ACh release in the frontal cortex.

BETA CATENIN TRANSGENIC MICE SHOW ENDOGENOUS MOOD STABILIZER-LIKE BEHAVIORS Einat, H.; Gould, T.D.; Eberhart, C.G.; Manji, H.K. Laboratory of Molecular Pathophysiology, NIMH, NIH, DHHS. Lithium (Li) inhibits the enzyme glycogen synthase kinase-3 (GSK-3) at therapeutic concentrations. One of the targets of GSK-3 is the transcription factor b-catenin. GSK-3 phosphorylates b-catenin leading to its degradation and inhibition of GSK-3. We utilized transgenic (Tg) mice to investigate the behavioral consequences of b-catenin overexpression. Western blot was utilized to measure b-catenin levels and routine behavioral tests of basic neurological function, motor and spatial learning. After we found no differences in these measures we tested the mice in models for affective-like behaviors including anxiety depression and mania models. Western blot analysis revealed significant expression of Tg b-catenin in the cortex and hippocampus, low expression in the cerebellum and none in other body tissues. B-catenin Tg mice show no gross neurological deficits, normal locomotion on a large open field, normal motor learning as observed with repeated accelerating rotarod, and normal spatial learning in a Morris water maze. However, Tg mice demonstrated decreased depression-like behavior as shown by decreased immobility time in the Forced Swim Test and decreased manic-like behavior as shown by decreased amphetamine-induced hyperactivity. No effects of transgene were shown in measures of anxiety-like behaviors. As b-catenin Tg mice have behavior that is both antidepressant-like and antimanic-like, the data is consistent with the hypothesis that Li may exert its mood stabilizing effects through inhibition of GSK-3. These results support the notion that novel small-molecule GSK-3 inhibitors may be useful for the treatment of bipolar disorder.

SLEEP RHYTHMICITY AND HOMEOSTASIS IN MICE WITH TARGETED DISRUPTION OF mPERIOD GENES. P.J. Shiromani1 and D.R. Weaver2. 1 VA & Harvard Med School, West Roxbury, MA, and 2 U Mass Med School, Worcester, MA. In mammals the timing of sleep and wakefulness is regulated by the suprachiasmatic nucleus (SCN). At the core of the circadian clock mechanism is a heterodimeric complex consisting of CLOCK and BMAL1 that drives expression of three Period (in mice, mPer1-3) and two cryptochrome (mCry1, mCry2) genes; PER/CRY complexes then inhibits CLOCK:BMAL1 activity (Reppert and Weaver, Nature 418: 935, 2002). An important unanswered question is whether the same genes that regulate the circadian clock might have also evolved to regulate the amount of sleep and wakefulness. The role of mCry in sleep regulation has been determined. Since mCry interacts with mPer to regulate circadian rhythms here we examine the role of the mouse Period (mPer) genes

on the rhythmic and homeostatic regulation of sleep. In entrained conditions, when averaged over the 24h period, there were no significant differences in waking, slow wave sleep (SWS) or REM sleep between mPer1, mPer2, mPer3, mPer1-mPer2 double mutants and wildtype (WT) mice. After 6h (ZT 6-12) sleep deprivation the mPer mutants exhibited increased sleep drive indicating an intact sleep homeostatic response in the absence of the mPer genes. In free-run conditions the mPer1-mPer2 double mutants became arrhythmic, but they continued to maintain their sleep levels even after 36d in free-running conditions. mPer 1 and mPer 2 but not mPer 3 represent key elements of the molecular clock in the SCN. Here we found that the mPer genes are not required for appropriate regulation of the daily amounts of waking, SWS or REM sleep. Research supported by the VAMC, NS30140, NS39303, AG15853, AG09975, and MH55772.

ABNORMALLY EXCESSIVE CORTICAL DENDRITIC BRANCHING IN A KNOCKOUT MOUSE MODEL OF THE FRAGILE X MENTAL RETARDATION SYNDROME. Mervis, R.F.1 2, Bachstetter, A.D.2, Ather,T.3, Maloney,T.3, Cupples,A.3, Toth, M.4 1Center of Excellence for Aging and Brain Repair, Dept. Neurosurgery, University of South Florida College of Medicine, Tampa, FL 33612, 2NeuroStructural Research Labs, Tampa, FL 33612; 3College of Arts & Sciences, USF, Tampa, FL 33512; 4Dept. Pharmacology, Weill Medical College of Cornell University, NY, NY 10021. Fragile X syndrome is the most common cause of inherited mental retardation and is caused by a mutation in the FMR1 gene leading to absence of the fragile X mental retardation protein (FMRP). Knockout of the gene associated with Fragile X, Fmr1, results in mice with abnormalities analogous to human symptoms. Neuroanatomical findings include an excess of abnormally thin, immature dendritic spines. FMRP may play a role in the normal process of dendritic spine growth and pruning of excess immature synapses. The impact of Fmr1 deletion on development of dendritic branching is poorly understood and is the focus of this study. Using Golgi impregnated neurons, we evaluated dendritic arborization of layer II/III pyramids of the parietal cortex of 10 week-old fragile X mice. Coronal blocks of the parietal cortex from fmr-1 knockout mice and WT controls (FVB/NJ) were stained using the Rapid Golgi method (N=5 per group). From coded slides, 5-6 layer II/III pyramidal neurons were randomly selected. Camera lucida drawings of the basilar tree were made of each neuron. Sholl analysis showed that the Fragile X mice had significantly more dendritic material throughout the extent of the basilar tree ($p = 0.0002$, Wilcoxon test). Estimated total dendritic length was 28% longer ($p=0.001$, unpaired T test) and branching complexity was greater. These findings suggest that Fragile X mice may have abnormalities of developmental pruning of both branching and spines which would result in anomalous processing of information in cortical circuits. This would contribute to the cognitive dysfunction and behavioral problems associated with Fragile X syndrome.

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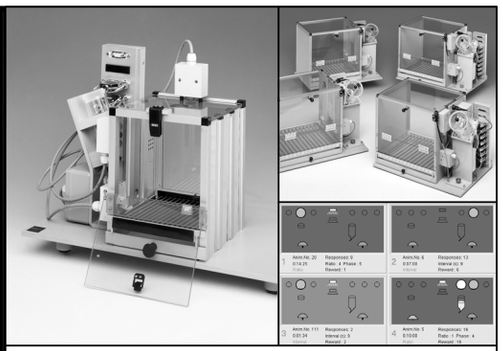

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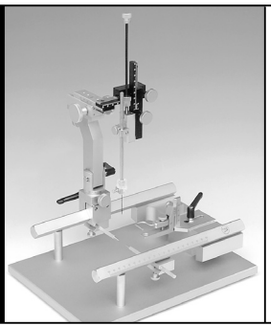

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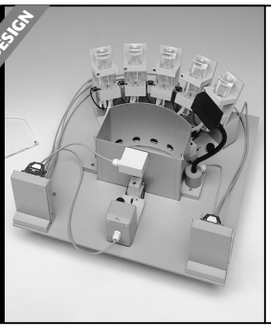

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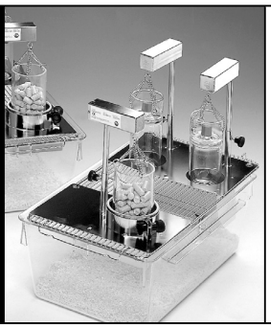

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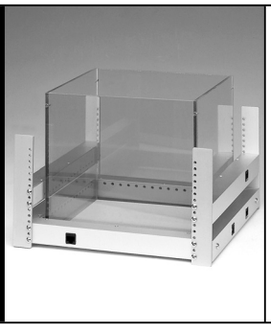

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NOTE: All presentations will be held in the Big Pine-Conch-Duck
Sections of the Keys Ballroom unless otherwise noted.

Tuesday, June 15:

8:30-6:00	Satellite: Defense Behavior – *Coral Reef Room*

Wednesday, June 16:

8:30-5:00	Satellite: Defense Behavior – *Coral Reef Room*
8:30-5:00	Satellite: Nicotine as a Therapeutic Agent – *Big Pine-Conch Room*
11:30-5:30	Registration – *Keys Ballroom Patio*
	Exhibitors Display – *Fiesta Plantation Room*
6:00-7:00	Opening Reception – *West Lawn*
7:00-7:15	Welcoming Remarks: Robert Blanchard
7:15-8:15	Keynote Speaker: Michael Davis

Thursday, June 17:

7:30-8:30	Continental Breakfast - *Keys Ballroom Patio*
	Exhibitors Display – *Fiesta Plantation Room*
8:30-10:30	Symposium 1: Factors influencing the acceleration and delay of aging
10:30-10:45	Refreshment Break/Exhibitors Display – *Fiesta Plantation Room*
10:45-11:45	Recognition of Local Scientist and Keynote Speaker: Paul Sanberg
11:45-1:15	Council Meeting – *Sea Breeze Room*
1:00-2:00	NIH Grant Workshop: Israel Lederhendler
2:00-4:00	Student Workshop: Student career development symposium
4:00-5:30	Student Travel Award Slide Blitz
5:30-7:30	Poster Session 1/Refreshments – *Grand Ballroom*

Friday, June 18:

7:30-8:30	Continental Breakfast - *Keys Ballroom Patio*
	Exhibitors Display – *Fiesta Plantation Room*
8:30-10:30	Symposium 2: Modeling abnormal brain and behavior development
10:30-10:45	Refreshment Break - *Keys Ballroom Patio*
	Exhibitors Display - *Fiesta Plantation Room*
10:45-11:45	Presidential Address: Robert Blanchard
11:45-1:30	Free time
1:30-3:30	Symposium 3: Estrogen: Old hormone, new tricks
5:00-7:00	Poster Session 2/Refreshments – *Grand Ballroom*

Saturday, June 19:

7:30-8:30	Continental Breakfast - *Keys Ballroom Patio*
	Exhibitors Display – *Fiesta Plantation Room*
8:30-10:30	Symposium 4: From complex phenotypes to genes
10:30-10:45	Refreshment Break - *Keys Ballroom Patio*
	Exhibitors Display - *Fiesta Plantation Room*
10:45-11:45	Keynote Speaker: George Koob
11:45-3:30	Free time
3:30-4:45	Oral Session 2: Chemistry and Behavior
4:45-5:30	Business Meeting – *Big Pine*
7:00-10:00	Banquet – *Big Pine/Conch/Duck/Fiesta Ballroom*
	Presentation of Travel Awards

Sunday, June 20:

7:30-8:30	Continental Breakfast - *Keys Ballroom Patio*
	Exhibitors Display – *Fiesta Plantation Room*
8:30-10:30	Symposium 5: Introduction to behavioral measures of impulsivity
10:30-10:45	Refreshment Break - *Keys Ballroom Patio*
	Exhibitors Display - *Fiesta Plantation Room*
10:45-12:15	Oral Session 3: Development, Differences & Disease Models
12:15	Adjourn

IBNS Central Office

Marianne Van Wagner, Executive Coordinator
8181 Tezel Road, #10269
San Antonio, TX 78250 USA
Tel.: (830) 796-9393
Fax: (830) 796-9394
Email: ibns@ibnshomepage.org
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