

International Behavioral Neuroscience Society



Program/Abstracts

**April 23-27, 2003
San Juan, Puerto Rico**

**Abstracts of the International Behavioral Neuroscience
Society, Volume 12, April 2003**

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CONTENTS

Abstracts	21-65
Acknowledgments	5
Advertisements	70-80
Author Index	66-69
Exhibitors/Sponsors	3
Program/Schedule	7-20
Travel Awards	2

Dear Fellow Behavioral Neuroscientists,

Welcome to the Twelfth Annual Meeting of the International Behavioral Neuroscience Society. On behalf of the Officers, Council, Program Committee, and membership of IBNS, I want to convey our pleasure that you are joining us this year in beautiful San Juan. Our colleagues from Puerto Rico that served on the Local Organizing Committee, under the very capable leadership of Juan Carlos Jorge, have arranged the excellent conference facilities. We thank them for their warm hospitality in hosting our international scientific conference.

A very special thanks is due to Tim Moran and his Program Committee. They have succeeded in putting together an exciting and diverse program. We have excellent keynote speakers and six special symposia representing the exciting breadth of research within behavioral neuroscience. Once again, Marianne Van Wagner, IBNS Executive Coordinator, has done a magnificent job in managing the many issues related to running our annual meeting.

While I hope to see you at many of the interesting sessions, there are several features of the program that I do want to call to your attention. First, we will have a special symposium (Thursday afternoon) in which our student travel award winners will give brief oral presentations. I urge you to attend and give support to the future leaders of our society. Second, there are some new features on our program this year. One involves an outreach program for local high schools that will take place on Wednesday. Another new program event is a student workshop on scientific ethics scheduled for Friday at lunchtime. In addition, we will have visitors from the University of Puerto Rico attending the meeting on Thursday. Third, I hope that you can attend the IBNS Business Meeting (Saturday late afternoon). During this meeting, discussions emerge about future meeting venues and other society business. It is an opportunity to express your opinions about your society. Fourth, I call your attention to the Myers Lifetime Achievement Award presentation - which launches our meeting this year - and will honor Dr. Joe Huston. Finally, I hope to see all of you at the banquet on Saturday evening, which promises to be a dramatic spectacle in old San Juan (be sure not to miss the bus!). In addition to presenting the student travel awards, we will honor a local scientist, Dr. Mark Miller, for his distinguished research in behavioral neuroscience.

If you are not already a member of IBNS, you are cordially invited to sign up at the registration desk here or after the meeting through the IBNS website (www.ibnshomepage.org). We hope to welcome you again to future IBNS meetings.

In closing, it has been an honor to serve as your IBNS President this year. Our society is strong and is growing - moreover, it occupies a critical niche in the neuroscientific community. I look forward to welcoming each of you to our Twelfth Annual Meeting.

Mark A. Geyer
IBNS President

We are pleased to announce the recipients of the IBNS Travel Awards for the 2003 meeting in San Juan, Puerto Rico. 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

Dr. Elissa J. Chesler, *University of Tennessee Health Sci. Ctr., USA*

Dr. Haim Einat, *NIMH, USA*

Dr. Susan Powell, *University of California, San Diego, USA*

Graduate

Ms. Suzanne A. Henry, *University of California at San Diego, USA*

Ms. Anna Lee, *Dalhousie University, Canada*

Mr. Yann S. Mineur, *University of Massachusetts Medical School, USA*

Ms. Tammy Moscrip, *Columbia University, USA*

Mr. Christopher Nelson, *The Ohio State University, USA*

Ms. Itzel Orduna, *Rutgers University, USA*

Dr. Wendy Portillo, *Centro De Neurobiología, Mexico*

Ms. Lianne Stanford, *Dalhousie University, Canada*

Mr. Martin Woodlee, *The University of Texas at Austin, USA*

Undergraduate

Ms. Tori Schaefer, *Cincinnati Children's Hospital Research Foundation, USA*

Student Travel awardees are presenting orally either in the Travel Award Blitz or in a regular scheduled session. They will also have their research presented in a poster session.

The IBNS would like to express our gratitude to the following organizations who have given financial support to the 12th 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
University of Puerto Rico
EPsCOR Program and Center for Molecular, Cellular, and
Behavioral Neuroscience Program (NIH-COBRE)
Puerto Rico Tourism Company
Puerto Rico Convention Bureau
Caribbean Wine and Spirits

EXHIBITORS/SPONSORS

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 12th International Behavioral Neuroscience Society Conference:

Annual Reviews
Brinkmann Eppendorf
Clever Sys. Inc.
Coulbourn, Inc.
Elsevier Science, Inc.
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Research Diets, Inc./BioDAQ
San Diego Instruments
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T S E Technical & Scientific Equipment GMBH
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 San Juan meeting.

MEMBER CONTRIBUTIONS OVER \$100

Sally Anderson
Jacqueline Crawley
Mark A. Geyer
Robert D. Myers
Michael L. Woodruff

MEMBER CONTRIBUTIONS

Joanne Berger-Sweeney
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Xuming Wang
Daniel Widzowski
John W. Wright
Betty Zimmerberg

ACKNOWLEDGMENTS

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

PROGRAM COMMITTEE:

Tim Moran (Chair), Markus Heilig (Co-Chair), Linda Spear, Steve Dunnett, Mark Geyer, Joseph Huston, Alain Gratton, Athina Markou, Sue Carter, Gary Coover, Elissa Chesler (Student).

LOCAL ORGANIZING COMMITTEE:

Juan Carlos Jorge (Chair), Madeline Valentin, Jorge Miranda, Annabell Segarra, Glenda Corretjer.

EDUCATION AND TRAINING COMMITTEE:

Kyle Frantz (Chair), John Rosecrans (Co-Chair), Deborah Colbern, Laura Ricceri, Robert Almlı, Robert Gerlai, Francisco Gonzalez-Lima, Vickie Risbrough (Student).

SCIENTIFIC PROGRAM

KEYNOTE SPEAKERS

- **JEFFREY GRAY**, Institute of Psychiatry, London, UK
Implications of synesthesia for functionalism: Theory and experiments
- **ANN KELLEY**, University of Wisconsin-Madison Medical School, Madison, WI, USA
Cortico-striatal-hypothalamic networks and motivation for food: Integration of cognition, reward and energy

PRESIDENTIAL ADDRESS

Mark A. Geyer, *Human, rat and mouse models of sensorimotor gating deficits in schizophrenia*

SPECIAL SYMPOSIA

- **Prenatal cocaine and attentional processes: Evidence for teratogenic effects on developing catecholamine systems.** Chair: Charles F. Mactutus, University of South Carolina, Columbia, SC, USA
- **Nonlinear and advanced behavioral assessment methods and their implications for behavioral neuroscience.** Chair: Joseph P. Huston, University of Dusseldorf, Dusseldorf, Germany
- **Animals models of depression: Recent findings.** Chair: Athina Markou, The Scripps Research Institute, La Jolla, CA, USA.
- **Neurobiology of cognition in laboratory animals.** Chair: Martin F. Sarter, The Ohio State University, Columbus, OH, USA
- **Role of neurosteroids in the pharmacology of ethanol.** Chair: Giovanni Biggio, University of Cagliari, Cagliari, Italy
- **Dissecting behavior with molecular genetics.** Chairs: Byron C. Jones, Pennsylvania State University, University Park, PA, USA and Pierre Mormède, Inserm-INRA-Universite de Bordeaux II, Bordeaux, France

STUDENT WORKSHOP ON SCIENTIFIC ETHICS

The workshop will include speakers Martin Paulus, Robert Adamec, Joanne Berger-Sweeney, Nancy Ostrowski and Susan Powell who will introduce the need for instruction and open debate of scientific ethics followed by small group discussions. Lunch will be provided.

UPR HIGH SCHOOL OUTREACH SEMINAR

University of Puerto Rico High School seniors have been invited to come for a special seminar including a lecture on drug abuse by Dr. Annabelle Segarra followed by a science and society ethics workshop run by graduate student members. Lunch will be provided.

The Workshop and Seminar are sponsored by a grant from the Survival Skills and Ethics Program at the University of Pittsburgh.

NOTE: All presentations, meetings, satellites, posters will be held in the **International Ballroom** unless otherwise noted. Presenting authors are indicated by **bold** type.

Wednesday, April 23:

- 10:00-2:00 **High School Outreach Seminar** - *International Ballroom*
- 1:00-4:00 **Registration** – *Foyer - International Ballroom*
Group Excursion - City Tour and Bacardi Rum Distillery (Registration separate - cost \$36)
- 5:00-5:30 **Welcoming Remarks: Mark A. Geyer**
- 5:30-6:00 **Marjorie A. Myers Lifetime Achievement Award in Behavioral Neuroscience: Joseph P. Huston**, University of Dusseldorf, Dusseldorf, Germany. NEURONAL HISTAMINE: THE NEGLECTED NEUROTRANSMITTER AND ITS FUNCTIONS. *Introduction: Mark A. Geyer*
- 6:00-7:00 **Keynote Speaker: Jeffrey Gray**, Institute of Psychiatry, London, UK. IMPLICATIONS OF SYNESTHESIA FOR FUNCTIONALISM: THEORY AND EXPERIMENTS. *Introduction: Mark A. Geyer*
- 7:00-8:30 **Reception** – *Almond Tree* (outside, through lighted archway, *Los Arcos*, adjacent to *Fantasy Pool*)

Thursday, April 24:

- 7:00-8:00 **Continental Breakfast/Exhibitors Display** – *International Ballroom*
- 8:00-10:00 **Symposium 1: Prenatal cocaine and attentional processes: Evidence for teratogenic effects on developing catecholamine systems.** *Chair: Charles F. Mactutus, University of South Carolina, Columbia, SC, USA*
- 8:00 LASTING EFFECTS OF PRENATAL COCAINE EXPOSURE ON SUSTAINED AND SELECTIVE ATTENTION AND REACTIVITY TO ERRORS. **Strupp, B.J.**; Gendle, M.H.; Morgan, R.E.; Garavan, H.; White, T.L.; Strawderman, M.S.; Mactutus, C.F.; Booze, R.M., Levitsky, D.A.
- 8:30 DOPAMINERGIC NEUROTRANSMISSION FOLLOWING PRENATAL IV COCAINE EXPOSURE. **Booze, R.M.**; Hasselrot, U.; Salvatore, M.F.; Hudspeth, O.; Gerhardt, G.A.; Strupp, B.J.; Snow, D.M.; Welch, M.A.; Mactutus, C.F.

- 9:00 EARLY PRENATAL COCAINE AND TERATOGENIC EFFECTS ON THE LC AS REVEALED IN BEHAVIOR AND ANATOMY. **Mactutus, C.F.**; Hasselrot, U.; Strupp, B.J.; Snow, D.M.; Welch, M.A.; Booze, R.M.
- 9:30 PRENATAL COCAINE EXPOSURE COMPROMISES OUTGROWTH POTENTIAL IN DEVELOPING LOCUS COERULEUS NEURONS. **Snow, D.**; Carman, H.; Smith, J.; Welch, M.; Booze, R.; Mactutus, C.
- 10:00-10:30 **Refreshment Break/Exhibitors Display**
- 10:30-12:00 **Oral Session 1: Stress and Anxiety.** *Chair: Juan Carlos Jorge*
- 10:30 SEX-SPECIFIC BEHAVIORAL EFFECTS OF ANABOLIC STEROIDS IN MICE. **Barreto-Estrada, J.L.**; Barreto, J.; Fortis, A.; Fortis, Y.; Rojas, Y.; Corretjer, G.; Jorge, J.C.
- 10:45 AVERSION AND CONDITIONING: THE CASE OF PREDATOR ODORS. **Blanchard, D.C.**; Markham, C.; Yang, M.; Hubbard, D.; Blanchard, R.J.
- 11:00 THE RAT EXPOSURE MODEL: A NOVEL MODEL OF RISK ASSESSMENT, AVOIDANCE, AND FREEZING FOR MICE. **Blanchard, R.J.**; Yang, M.; Augustsson, H.; Blanchard, D.C.
- 11:15 AGGRESSIVE BEHAVIOR AND UNPREDICTABLE CHRONIC MILD STRESS IN MICE: INTERACTIONS AND LIMITATIONS. **Mineur, Y.S.**; Prasol, D.J.; Belzung, C.; Crusio, W.E.
- 11:30 CENTRAL ADMINISTRATION OF A NEUROSTEROID INTO THE BASOLATERAL AMYGDALA MODIFIES ANXIETY IN AN ESTROGEN-DEPENDENT MANNER. **Pérez-Acevedo, N.L.**; García, E.; Jorge, J.C.
- 11:45 NEUROENDOCRINE DEVELOPMENT OF RHESUS MACAQUE INFANTS DURING THEIR FIRST TWO YEARS OF LIFE: EFFECTS OF SEX AND EARLY EXPERIENCE. **Maestriperi, D.**
- 12:00-2:00 **Council Meeting - Orquidea 1**
- 12:00-2:00 **Free time**
- 2:00-3:00 **Presidential Address:** Mark A. Geyer, HUMAN, RAT AND MOUSE MODELS OF SENSORIMOTOR GATING DEFICITS IN SCHIZOPHRENIA. *Introduction: Juan Carlos Jorge.*
- 3:00-3:15 **Refreshment Break/Exhibitors Display**
- 3:15-5:35 **Student Travel Award Blitz:** *Chair: Timothy H. Moran*
- 3:15 INTRACELLULAR SIGNALING PATHWAYS IN BIPOLAR DISORDER. **Einat, H.** †; Yuan, P.X.; Chen, G.; Dogra, S.; Manji, H.K.

- 3:25 SEX DIFFERENCES IN PPI OF MICE LACKING NR3A SUBUNITS. **Brody, S.A.** †; Nakanishi, N.; Lipton, S.A.; Geyer, M.A.
- 3:35 OBSERVATIONS OF UNUSUAL BEHAVIOR IN CALIFORNIA MICE, PEROMYSCUS CALIFORNICUS. **Lee, A.W.** †; Brown, R.E.
- 3:45 A NONHUMAN PRIMATE MODEL OF THE ANTEROGRADE AND RETROGRADE AMNESIA PRODUCED BY CONVULSIVE TREATMENT. **Moscrip, T.D.** †; Terrace, H.S.; Sackeim, H.A.; Lisanby, S.H.
- 3:55 PREFRONTAL REGULATION OF POSTERIOR PARIETAL ACETYLCHOLINE RELEASE. **Nelson, C.L.** †; Sarter, M.; Bruno, J.P.
- 4:05 CONDITIONED PLACE PREFERENCE IN NON COPULATING MALE RATS. **Portillo, W.** †; Camacho, F.J.; Paredes, R.G.
- 4:15 THE EFFECT OF A SINGLE VERSUS REPETITIVE PAIN EXPERIENCE DURING INFANCY ON ANXIETY AND SPATIAL LEARNING IN JUVENILE MICE. **Stanford, L.** †; Darrah, M.; Kelly, C.; Schellinck, H. M.
- 4:25 DISTINCTIVE BEHAVIORAL PROFILES IN ANIMAL MODELS OF PARKINSON'S DISEASE, STROKE, AND TRAUMATIC BRAIN INJURY. **Woodlee, M.T.** †; Fleming, S.M.; Schallert, T.
- 6:00-8:00 **Wine and Cheese/Exhibitors Display**
- 6:00-8:00 **Poster Session I: International Ballroom**
Topics: Modeling Neurodegenerative and Psychiatric Disorders, Learning and Memory, Drugs of Abuse, Attention, Education.
1. GD3 SYNTHASE KNOCKOUT MICE ARE RESISTANT TO β AMYLOID BINDING AND β AMYLOID-INDUCED NEUROTOXICITY. **Olaghere-DaSilva, U.**; Bernardo, A.; Zhao, J.; Hipkens, S.; Bruchey, A.; McDonald, M.
 2. FOLATE DEFICIENCY INDUCES HIPPOCAMPAL CELL DEATH AND EXACERBATES MEMORY DEFICITS IN APP TRANSGENIC MICE. **Bernardo, A.**, Olaghere-DaSilva, U., Zhao, J., Hipkens, S., McDonald, M.
 3. DEPRESSION IN A GROUP OF PUERTO RICAN WOMEN WITH PARKINSON'S DISEASE. **Pita, I.**; Serrano, C.; Wojna, V.
 4. IMPLICIT LEARNING IN AN ANIMAL MODEL OF HUNTINGTON'S DISEASE. **Jay, J.R.D.**; Dunnett, S.B.
 5. DISTINCTIVE BEHAVIORAL PROFILES IN ANIMAL MODELS OF PARKINSON'S DISEASE, STROKE, AND TRAUMATIC BRAIN INJURY. **Woodlee, M.T.**; Fleming, S.M.; Schallert, T.
 6. INTRACELLULAR SIGNALING PATHWAYS IN BIPOLAR DISORDER. **Einat, H.**; Yuan, P.X.; Chen, G.; Dogra, S.; Manji, H.K.

7. IMPULSIVITY AND IMPAIRED ATTENTION IN A MOUSE MODEL OF ATTENTION DEFICIT HYPERACTIVITY DISORDER. **Miller, L.R.**; Siesser, W.B.; McDonald, M.P.
8. ABNORMAL ATTENTION AND MOTIVATION IN A MOUSE MODEL OF RESISTANCE TO THYROID HORMONE. **Siesser, W.**; Cheng, S.-Y.; McDonald, M.
9. BEHAVIOR, BRAIN METABOLISM AND D1 RECEPTOR EXPRESSION CHANGES FOLLOWING REPEATED TREATMENT WITH METHYLPHENIDATE IN ADHD ANIMAL MODEL. Viggiano, D.; Vallone, D.; Ruocco, L.A.; **Sadile, A.G.**
10. PRENATAL INHIBITION OF ENDOCANNABINOID REUPTAKE REDUCES ACTIVITY AND MODIFIES THE UNBALANCE BETWEEN MESOSTRIATAL AND MESOCORTICOLIMBIC DOPAMINE SYSTEMS IN THE NAPLES HIGH EXCITABILITY RATS. Viggiano, D.; Ruocco, L.A.; Pignatelli, M.; **Sadile, A.G.**
11. NOVEL MULTIPLE EXPERIENCE PARADIGM (MEP): A MODEL FOR NEUROPSYCHIATRIC DISEASE? **Al Banchaabouchi, M.**; Pereira, L.; Pagán, J.; Pérez, R.; Peña de Ortiz, S.
12. HABENULAR LESIONS CAUSE COGNITIVE IMPAIRMENTS IN RATS: IMPLICATIONS FOR SCHIZOPHRENIA. Lecourtier, L.; Neijt, H.; **Kelly, P.H.**
13. VALIDATION OF MICROARRAY DATA AND DETERMINATION OF SPECIFIC HIPPOCAMPAL SUBREGIONS INVOLVED IN LONG-TERM MEMORY BY LASER CAPTURE MICRODISSECTION AND QUANTITATIVE REAL TIME PCR. **Vivas-Mejía, P.**; Robles, Y.; Felix, J.; Ortiz-Zuazaga, H.G.; Peña de Ortiz, S.
14. THE DNA LIGASE INHIBITOR ara-CTP BLOCKS LONG-TERM MEMORY OF CONDITIONED TASTE AVERSION AND SPATIAL LEARNING. **Wang, J.**; Ren, K.; Ramos, X; Pérez, J; Flores, G.; Pagan, J.; Peña de Ortiz, S.
15. MECHANISMS OF LEAD-MEDIATED COGNITIVE IMPAIRMENT IN THE ADULT RAT BRAIN. **Vázquez, A.**; Peña de Ortiz, S.
16. MOLECULAR CHARACTERIZATION OF CREB IR TRANSGENIC SYSTEM IN MICE DURING MEMORY AND LEARNING PROCESSES. **Chévere, I.**; Wang, J.; Labault, J.; Silva, A.J.; Peña de Ortiz, S.
17. NEUROGRANIN ENHANCES THE HIPPOCAMPUS-DEPENDENT LEARNING AND MEMORY. **Huang, F.L.**; Wu, J.; Kolker, D.E.; Huang, K.-P.
18. NUCLEOTIDE PHOSPHODIESTERASE INHIBITORS AND MEMORY IN THE RAT. Giorgi, M.; Modica A.; Pompili, A.; Pacitti, C.; **Gasbarri, A.**
19. OREXIN - A ENHANCES DENTATE GRANULE CELL LONG TERM POTENTIATION. Smith, B.G.; **Wayner, M.J.**; Armstrong, D.L.; Phelix, C.F.; Oomura, Y.
20. LINKING THE P300 EVENT RELATED POTENTIAL IN RATS TO PRIMARY AND CONDITIONED REINFORCING STIMULI. **Schneider, B.**; Klipec, W.D.; Franck, L.
21. A NONHUMAN PRIMATE MODEL OF THE ANTEROGRADE AND RETROGRADE AMNESIA PRODUCED BY CONVULSIVE TREATMENT. **Moscrip, T.D.**; Terrace, H.S.; Sackeim, H.A.; Lisanby, S.H.

22. GLUCOSE TRANSPORTER PLASTIC CHANGES IN THE HIPPOCAMPUS FOLLOWING MEMORY PROCESSING. **Messier, C.**; Choeiri, C.; Staines, W.M.
23. RATS WITH DORSAL, BUT NOT COMPLETE, HIPPOCAMPAL LESIONS SHOW TEMPORALLY GRADED RETROGRADE AMNESIA ON A PLUS MAZE SPATIAL TASK. **Means, L.W.**; Hoane, M.R.
24. EFFECT OF BEHAVIORAL DESPAIR ON NAVIGATIONAL LEARNING IN FEMALE WISTAR RATS. **Canbeyli, R.**; Aksoy, A.; Kumru, G.; Yapici, N.; Acik, A.; Baran, B.; Ozcelik, S.
25. OPERANT ANALYSIS OF COGNITIVE BEHAVIOURS DEPENDENT UPON FRONTOSTRIATAL AND HIPPOCAMPAL SYSTEMS OF THE BRAIN. **Sloan, H.**; Dunnett, S.
26. D1, BUT NOT D2, D3, OR D4 RECEPTORS, ARE ESSENTIAL FOR DISRUPTION OF PREPULSE INHIBITION BY COCAINE IN MICE. **Lehmann-Masten, V.**; Ralph-Williams, R.; Klamer, D.; Otero-Corchon, V.; Grandy, D.; Low, M.J.; Geyer, M.A.
27. HALOPERIDOL ANTAGONISES AMPHETAMINE INDUCED DISRUPTION OF LATENT INHIBITION IN CONDITIONED TASTE AVERSION. **Russig, H.**; Kovacevic, A.; Murphy, C.A.; Feldon, J.
28. DIFFERENTIAL EFFECTS OF METHAMPHETAMINE AND COCAINE ON RATS' DISCRIMINATION PERFORMANCE IN Y-MAZE AND TWO LEVER CHOICE PARADIGMS. **Dolezal, A.**; Klipec, W.D.; Mejia, R.
29. BLOCKADE OF THE MOTOR STIMULANT EFFECTS OF AMPHETAMINE BY GROUP I, GROUP II, AND GROUP III METABOTROPIC GLUTAMATE RECEPTOR LIGANDS IN THE RAT NUCLEUS ACCUMBENS: POSSIBLE INTERACTIONS WITH DOPAMINE RECEPTORS. **David, H.N.**, Abraini, J.H.
30. HIPPOCAMPAL SEROTONIN AND THE ACUTE BEHAVIORAL EFFECTS OF COCAINE: EVIDENCE FROM IN-VIVO MICRODIALYSIS STUDIES. Müller, C.P.; Carey, R.J.; **Huston, J.P.**
31. THE TIME COURSE OF EFFECTS FOLLOWING THE ADMINISTRATION OF METHYLENEDI OXYMETHAMPHETAMINE, 'ECSTASY', ON CENTRAL NERVOUS SYSTEM MONOAMINE CONTENT, PITUITARY ACTIVATION, AND ADRENAL OUTPUT ON POSTNATAL DAY 11 IN RATS. **Williams, M. T.**; Schaefer, T.L.; Ehrman, L.A.; Sah, R.; Gudelsky, G.A.; Vorhees, C.V.
32. U-69593, A KAPPA-OPIOID AGONIST, DECREASES COCAINE-INDUCED LOCOMOTOR ACTIVITY IN ESTROGEN PRIMED FEMALE RATS. **Puig-Ramos, A.**; Bruckman, W.J.; Santiago, G.S.; Segarra, A.C.
33. GENES ENCODING PROTEINS WITHIN THE NUCLEUS ACCUMBENS SUBREGIONS ARE AFFECTED BY REINSTATEMENT OF COCAINE-SEEKING BEHAVIOR. **Ramos, D.L.**; Félix, J.; Al-Banchaabouchi, M.; Menéndez, R.; Moulder, J.K.; Otero, J.M.; Jiménez, D.M.; Peña de Ortiz, S.; Maldonado-Vlaar, C.S.

34. DOPAMINE D3 RECEPTOR INVOLVEMENT ON SELECTIVE ATTENTION, IN THE RAT. Casarrubea, M.; Saia, V.; Sorbera, F.; **Crescimanno, G.**
35. EFFECTS OF MICROGRAVITY ON ORIENTING REACTION, IN THE RAT. Adamo, L.; Casarrubea, M.; Conti, M.; Fazio, G.; Adamo, A.; Mazzola, C.; **Crescimanno, G.**
36. VISUAL-MOTOR INTEGRATION: A MODIFIED LINE BISECTION TEST IN A NORMAL POPULATION. **Bloomer, R.**; Pezzulo, P.
37. PREFRONTAL REGULATION OF POSTERIOR PARIETAL ACETYLCHOLINE RELEASE. **Nelson, C.L.**; Sarter, M.; Bruno, J.P.
38. MODULATION OF CORTICAL ACETYLCHOLINE RELEASE BY NUCLEUS ACCUMBENS NMDA RECEPTORS. **Gatien, M.L.**; Sarter, M.; Bruno, J.P.
39. ORGANIZING A SATELLITE IBNS CLUB AT YOUR UNIVERSITY. **Risbrough, V.**; Evans, J.; Henry, S.; Ong, J.; Geyer, M.
40. THE HUMAN HPLC COLUMN: "MINDS-ON" NEUROSCIENCE FOR THE NEXT GENERATION. **Frantz, K.J.**; Rose, J.

Friday, April 25:

- 7:00-8:00 **Continental Breakfast/Exhibitors Display – International Ballroom**
- 8:00-10:00 **Symposium 2: Nonlinear and advanced behavioral assessment methods and their implications for behavioral neuroscience.** *Chair:* Joseph P. Huston, University of Dusseldorf, Dusseldorf, Germany
- 8:00 COMPLEXITY AND BEHAVIORAL ORGANIZATION IN RODENTS. **Paulus M.P.**; Powell S.B.; Geyer M.A.
- 8:20 MEASURING LOCOMOTOR PATTERNS IN DOPAMINE TRANSPORTER KNOCKOUT MICE. **Powell, S.** †; Paulus M.; Ralph-Williams, R.; Lehman-Masten, V.; Caron, M.; Geyer, M.
- 8:40 MOTOR BEHAVIOR IN WILD AND LABORATORY RODENTS: STRUCTURE OF ENVIRONMENT AFFECTS THE SPATIAL DISTRIBUTION BUT NOT THE LEVEL OF ACTIVITY OR THE TEMPORAL ORGANIZATION OF LOCOMOTION. **Eilam, D.**; Szechtman, H.
- 9:00 NON-LINEAR EFFECTS ON THE RETENTION OF AN AVOIDANCE RESPONSE INDUCED BY SHOCK LEVELS AND ANABOLIC STEROIDS. **Isaacson, R. L.**; Lewis, H. W. III.
- 9:20 A DYNAMICAL DISEASE MODEL OF STEREOTYPED BEHAVIOR: MEASURING COMPLEXITY AND REGULARITY. **Lewis, M.H.**; Bodfish, J.W.; Newell, K.M.
- 10:00-10:30 **Refreshment Break/Exhibitors Display**

- 10:30-12:00 **Oral Session 2: Ingestion.** *Chair: Susan Swithers*
- 10:30 EFFECTS OF GALANIN ON FEEDING BEHAVIOR IN THE MOUSE. **Wrenn, C.C.**; Holmes, A.; Saavedra, M.C.; Luo, M.; Sullivan, T.; Crawley, J.N.
- 10:45 INCENTIVE MOTIVATIONAL PROPERTIES OF ALIMENTARY AND SEXUAL STIMULI: FUNDAMENTAL DIFFERENCES. **Agmo, A.**
- 11:00 EFFECT OF NEUROPEPTIDE Y MICROINJECTED INTO THE PVN ON THE CONSUMPTION OF ETHANOL OR FOOD. Lucas, L.A.C.; **McMillen, B.A.**
- 11:15 INFUSING 5-HT_{2A} RECEPTOR ANTAGONISTS INTO THE BASOLATERAL AMYGDALA ENHANCES FEEDING. **Coscina, D.**; Parker, G.; Joshi, D.
- 11:30 β -ENDORPHIN PEPTIDE DERIVATIVES SUPPRESS ALCOHOL INTAKE IN THE N. ACCUMBENS OF P RATS. **Resch, G.E.**; Simpson, C.W.
- 11:45 EFFECTS OF MECAPTOACETATE ON DIET CHOICE IN JUVENILE RATS. **Swithers, S.E.**; McCurley, M.A.
- 12:00-3:00 **Student Workshop on Scientific Ethics** – *Lunch (for Workshop participants only) will served on the Ballroom Terrace followed by the Workshop in the International Ballroom.*
- 12:00-3:45 **Free time**
- 3:45-5:45 **Symposium 3: Animals models of depression: Recent findings.** *Chair: Athina Markou, The Scripps Research Institute, La Jolla, CA, USA.*
- 3:45 BEHAVIORAL AND PHYSIOLOGICAL RESPONSES TO CHRONIC MILD STRESSORS: GENDER AND STRAIN DIFFERENCES. **Bielajew, C.**; Konkle, A.T.M.; Kentner, A.C.; Baker, S.L.
- 4:05 DRUG WITHDRAWAL AS AN ANIMAL MODEL OF DEPRESSION. **Markou, A.**
- 4:25 EARLY DEPRIVATION IN MARMOSSET MONKEYS AND RATS AS ANIMAL MODELS OF DEPRESSION: LONG-TERM NEUROBEHAVIOURAL EFFECTS. Pryce, C.R.; Dettling, A.C.; Rüedi-Bettschen, D; **Feldon, J.**
- 4:45 MURINE MODELS OF DEPRESSION: UTILITY FOR KNOCKOUT AND TRANSGENIC BEHAVIORAL STUDIES. **Cryan, J.F.**
- 5:05 DOMINANT AND SUBMISSIVE BEHAVIOR IN RATS AS A MODEL OF MANIA AND DEPRESSION. **Malatynska, E.**; Crites, G.; Rapp, R.; Crooke, J.; Rosenthal, D.; Milewski, M.; Brenneman, D.
- 6:00-8:00 **Wine and Cheese/Exhibitors Display**

6:00-8:00 **Poster Session II: International Ballroom**

Topics: Anxiety and Stress, Sexual Behavior, Developmental Psychobiology, Neurotransmission, Alcohol, Nicotine and Behavioral Genetics.

41. INVOLVEMENT OF NEUROTRANSMITTERS IN THE ANXIOLYTIC ACTION OF PACAP 38 IN RATS. **Telegdy, G;** Adamik, A.
42. INHIBITION OF CORTICOSTERONE WITH METYRAPONE DELAYS EXTINCTION OF THE CONDITIONED EMOTIONAL RESPONSE (CER). **Hernández-Poudevida, P.;** McEwen, B.S.; Quirk, G.J.
43. LONG TERM MEMORY FOR EXTINCTION OF AUDITORY FEAR CONDITIONING REQUIRES PROTEIN SYNTHESIS. **Santini, E.;** Quirk, G.J.
44. STIMULATION OF INFRALIMBIC CORTEX SIMULATES FEAR EXTINCTION. **Vidal-Gonzalez, I.;** Milad, M.R.; Quirk, G.J.
45. THE VENTROMEDIAL PREFRONTAL CORTEX IS NECESSARY FOR RAPID CONSOLIDATION OF EXTINCTION LEARNING. **Lebron, K.;** Quirk, G.J..
46. CRF INCREASES STARTLE BUT NOT FEAR POTENTIATED STARTLE IN MICE. **Risbrough, V.B.;** Geyer, M.A.
47. KINDLING INDUCED LASTING INTERICTAL ALTERATIONS OF AFFECTIVE BEHAVIOR. **Adamec, R.**
48. CENTRAL INFUSION OF AN ANABOLIC STEROID INDUCES MODULATION OF AFFECTIVE COMPONENTS OF BEHAVIOR. **Rivera, J.C.;** Fernandez, M.; Delgado, C.; Jorge, J.C.
49. IMPAIRED EPISODIC OBJECT MEMORY AND INCREASED ANXIETY IN HDC KNOCKOUT MICE. **De Souza Silva, M.A.;** Dere, E.; Topic, B.; Spieler, R.E.; Haas, H.L.; Huston, J.P.
50. ESTROGEN MODULATES THE HEDONIC AND ANTI-ANXIETY PROPERTIES OF THE NEUROSTEROID 3 α DIOL. Marrero, J.; Lorenzini, I.; Garcia-Corbea, E.; Serrano, G.; **Jorge, J.C.**
51. MODULATORY EFFECTS OF ESTROGEN ON ANXIETY RELATED BEHAVIORS. **Lizardi, L.** and Jorge, J.C.
52. ACTIVITY-STRESS MODIFIES HIPPOCAMPAL MORPHOLOGY AND LOCUS COERULEUS FOS-IMMUNOREACTIVITY. Lin, S.M.; Glasper, E.R.; Campbell, T.; Kinsley, C.H.; **Lambert, K.G.**
53. CONDITIONED PLACE PREFERENCE IN NON COPULATING MALE RATS. **Portillo, W.;** Camacho, F.J.; Paredes, R.G.
54. SYNERGISTIC ACTIONS BETWEEN MATING AND CHEMICAL STIMULATION OF THE MEDIAL AMYGDALA (MEAPD): TOWARDS THE FORMATION OF A NEUROENDOCRINE MEMORY. **Lehmann, M.L.;** Erskine, M.S.

55. EXPRESSION OF THE FEMALE SEXUAL BEHAVIOR IN A MULTIPLE CHOICE TEST DURING THE ESTROUS CYCLE OF THE RAT. **Ferreira-Nuño, A.**; Morales-Otal, A.; Velázquez-Moctezuma, J.
56. NORADRENERGIC AFFERENTS TO MEDIAL AMYGDALA MODULATE MATING-INDUCED C-FOS EXPRESSION. **Carey, P.S.**; Erskine, M.S.; Cameron, N.
57. BOTH CHRONIC MILD STRESS AND BRAIN-STIMULATION REWARD INDUCE ESTRUS CYCLE DISRUPTIONS IN THE FEMALE RAT. **Konkle, A.T.M.**; Baker, S.L.; Kentner, A.C.; Santa-Maria Barbagallo, L.; Bielajew, C.
58. CHARACTERIZATION OF 50 KHZ VOCALIZATIONS IN MALE AND FEMALE RATS. **McGinnis, M.**; Vakulenko, M. Meas, S.
59. ENVIRONMENTAL ENRICHMENT REVERSES SPATIAL LEARNING AND MOLECULAR DEFICITS IN DEVELOPMENTAL LEAD NEUROTOXICITY. **Guilarte, T.R.**; Toscano, C.D.; McGlothan, J.L.; Weaver, S.A.
60. THE EFFECT OF A SINGLE VERSUS REPETITIVE PAIN EXPERIENCE DURING INFANCY ON ANXIETY AND SPATIAL LEARNING IN JUVENILE MICE. **Stanford, L.**; Darrah, M.; Kelly, C., Schellinck, H.M.
61. SELECTIVE BASAL FOREBRAIN CHOLINERGIC LESIONS ON POSTNATAL DAY 7 HAVE SHORT-TERM EFFECTS ON RAT PUPS'; BEHAVIOUR. **Scattoni, M.L.**; Calamandrei, G.; Puopolo, M.; Ricceri, L.
62. EARLY POSTNATAL STRESS AND ADULT BEHAVIORAL TESTING ALTER CORTICAL MORPHOLOGY IN MOUSE. **Jarvis, N.**; Watson, K.; Redding, C.; Hohmann, C.F.
63. SEX DIFFERENCES IN BEHAVIOR IN RESPONSE TO PRENATAL CHOLINE SUPPLEMENTATION. Brownlee, L.; Washington, K.; Hohmann, C.; **Berger-Sweeney, J.**
64. EFFECTS OF NEONATAL BILATERAL AMYGDALA LESIONS ON GROUP SOCIAL DYNAMICS IN ADULT RATS. **Kelly, S.J.**; Gerritts, M.A.F.M.; Wolterink-Donselaar, I.G.; van Ree, J.M.
65. ULTRASONIC VOCALIZATIONS ALTERED DUE TO TESTING TIME AND A CHANGE IN DIETARY PHYTOESTROGEN INTAKE DURING GESTATION AND NURSING. Kunkel, A.J.; **Becker, L.A.**
66. CENTRAL EFFECTS OF EARLY EXPERIENCE IN THE BORDERLINE HYPERTENSIVE RAT. **Kobsa, S.**; Sanders, B.J.; Anticevic, A.; and Dale, D.
67. ANABOLIC STEROIDS INDUCE SEX-SPECIFIC INHIBITION OF SOCIAL BEHAVIORS IN C57BL/6. **Barreto, J.**; Barreto-Estrada, J.; Corretjer G.; Fortis, Y.; Jorge, J.C.
68. EFFECT OF LESIONS TO THE DORSAL PREMAMMILLARY NUCLEUS ON DEFENSIVE BEHAVIORS. **Markham, C.M.**; Li, C.; Cuyno, C.; Blanchard, R.J.; Takahashi, L.K.; Blanchard, D.C.

69. HYPOCRETIN2-SAPORIN (HCRT2-SAP) LESIONS OF THE LATERAL HYPOTHALAMUS DOES NOT AFFECT THE ENTRAINED OR FREE-RUNNING RHYTHM OF CORE BODY TEMPERATURE. **Shiromani, P.J.**; Gerashchenko, D.; Blanco-Centurion, C.
70. ACTIONS OF CART ON NEURONAL ACTIVITY OF THE VENTRAL TEGMENTAL AREA IN RATS. **Sasaki, K.**; Otsubo, Y.; Ishibashi, M.; Oomura, Y.
71. FUNCTIONAL INTERACTIONS BETWEEN DOPAMINE ET GLUTAMATE NEUROTRANSMISSIONS. **David, H.N.**; Abbraini, J.H.
72. MEASUREMENT OF DRUG INDUCED CHANGES IN THE ELECTRICAL ACTIVITY OF ACUTE BRAIN SLICES FROM BLUEGILL SUNFISH AS A SURROGATE FOR FISH BEHAVIOR. **Rossi, J.**; McInturf, S.; McDougle, F.; Bekkedal, M.; Ritchie, G.
73. TARGETED GENETIC REDUCTION OF GABAA RECEPTOR $\alpha 2$ SUBUNITS REDUCES ETHANOL-INDUCED SPATIAL MEMORY IMPAIRMENTS IN MICE. **Berry, R.B.**; Chandra, D.; Homanics, G.E.; Matthews, D.B.
74. CHRONIC INTERMITTENT ETHANOL EXPOSURE IN ADOLESCENT RATS PRODUCES TOLERANCE TO ETHANOL-INDUCED SPATIAL MEMORY DEFICITS: AN INVESTIGATION OF POSSIBLE MOLECULAR MECHANISMS. **Silvers, J.M.**; Goodwin, S.B.; Sutter, T.R.; Morrow, A.L.; Matthews, D.B.
75. ALLOPREGNANOLONE NEUROGENESIS ALTERS ETHANOL'S EFFECT IN THE HIPPOCAMPUS. **Tokunaga, S.**; Morrow, A.L.; Matthews, D.B.
76. DOSES OF ESTRADIOL VALERATE (EV) AND FEMALE RATS' APPETITE FOR ALCOHOL. **Reid, L.D.**; Ledesma de la Teja, S.; Sanchez, M.A.; Reid, M.L.; Diaz-Trujillo A.; Prado-Alcala, R.A.
77. POSTCESSATION CHANGES IN FOOD SELECTION IN POSTMENOPAUSAL WOMEN. **Geiselman, P.J.**; Martin, P.D.; Copeland, A.L.; Ryan, D.H.; Bordelon, J.R.; Neal, J.L.
78. LONG TERM EFFECTS OF TRANSDERMAL NICOTINE ON MOOD AND SLEEP. **Haro, R.**; Drucker-Colín, R.
79. GENETIC AND BEHAVIORAL DIVERSITY OF MOUSE STRAINS AND SUBSTRAINS. **Bothe, G.**; Vedder, M.; Geistfeld, J.
80. TRANSGENIC MICE EXPRESSING A TRUNCATION MUTANT OF CBP EXHIBIT SPATIAL MEMORY DEFICITS. **Wood, M.**; Lombardi, T.; Park, A.; and Abel, T.
81. SEX DIFFERENCES IN PPI OF MICE LACKING NR3A SUBUNITS. **Brody, S.A.**; Nakanishi, N.; Lipton, S.A.; Geyer, M.A.
82. ALPHA4-CONTAINING NEURONAL NICOTINIC RECEPTORS MODULATE APPETITIVE LEARNING. **Wehner, J.M.**; Balogh, S.A.; Bowers, B.J.; Logue, S.F.; Ernisse, J.; Labarca, C.; Lester, H.A.

83. OBJECT EXPLORATION IN DARPP-32 KNOCKOUT MICE. **Heyser, C.J.**; Owens, C.H.; Pelletier, M.N.; Werner, J.L.; Fienberg, A.A.; Greengard, P.
84. BEHAVIORAL ANALYSIS OF MICE LACKING EXPRESSION OF NEURONAL OR ASTORCYTIC NFk-B. **Bramwell, J.**; Green, E.; Bethea, J.
85. BDNF CONDITIONAL MUTANTS EXHIBIT ALTERATIONS IN SEROTONIN (5-HT) NEUROTRANSMISSION. **Rios, M.**; Liu, R.; Lambe, E.; Jaenisch, R.; and Aghajanian, G.
86. OBSERVATIONS OF UNUSUAL BEHAVIOR IN CALIFORNIA MICE, PEROMYSCUS CALIFORNICUS. **Lee, A.W.**; Brown, R.E.
87. NONLINEAR BEHAVIOR DYNAMICS AS A DEPENDENT VARIABLE IN BEHAVIORAL PHARMACOLOGICAL STUDIES. Li, J.-S.; **Huston, J.P.**

Saturday, April 26:

- 7:00-8:00 **Continental Breakfast/Exhibitors Display – International Ballroom**
- 8:00-10:00 **Symposium 4: Neurobiology of cognition in laboratory animals.** *Chair:* Martin F. Sarter, The Ohio State University, Columbus, OH, USA.
- 8:00 RODENT COGNITION: DEFINING THE ISSUES. **Sarter, M.**
- 8:10 COGNITIVE PROCESSES IN SPATIAL LEARNING AND NAVIGATION. **Sutherland, R.J.**; Hamilton, D.A.
- 8:35 NEUROBIOLOGY OF PROCESSING CAPACITY: FROM RATS TO MONKEYS. **Turchi, J.**
- 9:00 FRONTO-EXECUTIVE FUNCTIONS IN RODENTS: NEURAL AND NEUROCHEMICAL SUBSTRATES. **Cardinal, R.N.**; Dalley, J.W.; Passetti, F.; Theobald, D.E.; Winstanley, C.A.; Robbins, T.W.
- 9:25 DISSOCIATING TIME AND EVENT MEMORY IN LABORATORY ANIMALS. **McDonald, M.P.**
- 10:00-10:30 **Refreshment Break/Exhibitors Display**
- 10:30-11:30 **Oral Session 3: Learning and Memory.** *Chair:* Joanne Berger-Sweeney
- 10:30 EFFECTS OF SUBSTANCE P AND NK1 RECEPTOR ANTAGONIST WIN 62.577 IN AMYGDALOID LEARNING MECHANISMS. **Lenard, L.**; Kertes, E.; Laszlo, K.

- 10:45 HIPPOCAMPAL MEDIATION IN AUDITORY PERCEPTUAL LEARNING. **Orduna, I.** †; Mercado, E; Gluck, M.
- 11:00 ESSENTIAL ROLE OF LEPTIN IN HIGHER BRAIN FUNCTION. **Oomura, Y.**; Aou, S.; Li, X.; Hori, N.; Wayner, M. J.; Armstrong, D. L.
- 11:15 THE EVERCHANGING CELLS OF WHALES. **Mercado III, E.**
- 11:30-1:15 **Free time**
- 1:15-3:15 **Symposium 5: Role of neurosteroids in the pharmacology of ethanol.** *Chair:* Giovanni Biggio, University of Cagliari, Cagliari, Italy.
- 1:15 ETHANOL-STIMULATED INCREASES IN NEUROACTIVE STEROIDS IN BRAIN. **Purdy, R.**; Vallee, M; O'Dell, L.; Alomary, A.; Fitzgerald, R.; Koob, G.
- 1:35 SOCIAL ISOLATION INCREASES THE STEROIDOGENIC EFFECT OF ETHANOL IN THE RAT BRAIN. **Biggio, G.**; Dazzi, L.; Serra, M.
- 1:55 MODULATION OF BRAIN NEUROACTIVE STEROIDS BY ENDOGENOUS AND EXOGENOUS GAMMA-HYDROXYBUTYRATE, A PUTATIVE THERAPEUTIC AGENT FOR ALCOHOL DEPENDENCE. **Concas, A.**; Porcu, P.; Sogliano, P.; Gupta, M.; Gibson, M.K.; Biggio, G.
- 2:15 INTERACTION BETWEEN ENDOGENOUS ALLOPREGNANOLONE LEVELS AND ETHANOL CONSUMPTION. **Finn, D.A.**; Sinnott, R.S.; Long, S.L.; Matthews, S.D.; Tanchuck, M.A.; Phillips, T.J.
- 2:35 STEROID NEUROGENESIS IS NECESSARY FOR ETHANOL-INDUCED COGNITIVE IMPAIRMENTS. **Matthews, D.B.**; Tokunaga, S.; Silvers, J.M.; Morrow A.L.
- 2:55 DISCRIMINATIVE STIMULUS EFFECTS OF NEUROSTEROIDS AND ETHANOL IN MICE, RATS AND MONKEYS. **Grant, K.A.**; Rogers, L.M.; Purdy, R.M.; Shannon, E.E.
- 3:15-3:30 **Refreshment Break/Exhibitors Display**
- 3:30-4:30 **Keynote Speaker: Ann Kelley.** University of Wisconsin-Madison Medical School, Madison, WI, USA. CORTICO-STRIATAL-HYPOTHALAMIC NETWORKS AND MOTIVATION FOR FOOD: INTEGRATION OF COGNITION, REWARD AND ENERGY. *Introduction: Timothy H. Moran.*
- 4:30-5:00 **Business Meeting - International Ballroom.**
- 7:00 **Banquet will be held at** La Arcada, Paseo La Princesa in Old San Juan. Transportation will be provided. Meet at 6:00 p.m. at the hotel's Main Entrance.
Presentation of Travel Awards
Recognition of Local Scientist: Dr. Mark Miller, Full Professor, Department of Anatomy and Interim Director of the Institute of Neurobiology, Medical Sciences Campus, University of Puerto Rico, San Juan- PR

Sunday, April 27:

- 7:00-8:00 **Continental Breakfast** – *International Ballroom*
- 8:00-10:00 **Symposium 6: Dissecting behavior with molecular genetics.** *Chairs:* Byron C. Jones, Pennsylvania State University, University Park, PA, USA and Pierre Mormède, Inserm-INRA-Universite de Bordeaux II, Bordeaux, France.
- 8:00 MARKER-ASSISTED SELECTION OF A NEUROBEHAVIORAL TRAIT RELATED TO BEHAVIORAL INHIBITION IN THE SHR STRAIN, AN ANIMAL MODEL OF ADHD. **Mormède, P.**; Moneva, E.; Bruneval, C.; Moisan, M.-P.
- 8:30 GENETIC DISSECTION OF ETHANOL-RELATED BEHAVIORS IN RATS DERIVED FROM HIGH- AND LOW CONSUMING LINES. **Jones, B.C.**; Terenina, E.; Moisan, M.-P.; Mormède, P.
- 9:00 KNOCKOUT/CONGENIC STRAINS AS TOOLS FOR MAPPING BEHAVIORAL TRAITS IN THE MOUSE. **Flaherty, L.**; Bolivar, V.J.; Cook, M.N.
- 9:30 TRANSCRIPTOME TO BEHAVIOR: GENE EXPRESSION PROFILING OF THE GAMMA-PKC NULL MUTANT MOUSE. **Radcliffe, R.A.**; Bowers, B.J.; Smith, A.; and Wehner, J.M.
- 10:00-10:30 **Refreshment Break**
- 10:30-12:00 **Oral Session 4: Genetic and neural injury models.** *Chair: Mikhail Pletnikov*
- 10:30 DISSECTING ALLELE-DEPENDENT MOTOR AND SLEEP BEHAVIOR IN A MOUSE LACKING TWO POTASSIUM CHANNELS. **Joho, R.H.**; Espinosa, F.; McMahon, A.; Marks, G.A.
- 10:45 GENETIC CORRELATIONS OF GENE EXPRESSION WITH NEURO-BEHAVIORAL TRAITS IN A RECOMBINANT INBRED MAPPING PANEL. **Chesler, E.J.** †; Wang, J.; Lu, L.; Qu, Y.; Manly, K.L.; Williams, R.W.
- 11:00 BEHAVIORAL AND NEUROCHEMICAL EFFECTS INDUCED BY SUBCHRONIC EXPOSURE TO 40 PPM TOLUENE IN RATS. **Berenguer, P.**; Soulage, C.; Perrin, D.; Péquignot, J.M.; Abbraini, J.H.
- 11:15 INFLUENZA INFECTION OF THE RAT BRAIN IN MODELING ABNORMAL BRAIN AND BEHAVIOR DEVELOPMENT. **Pletnikov, M.**; Rubin, S; Skapik, J; Moran, T.H.; Carbone, K.
- 11:30 ADMINISTRATION OF VARIOUS PSYCHOSTIMULANTS ON P11 CAUSES DIFFERENTIAL CHANGES IN CORTICOSTERONE AND MONOAMINE LEVELS 18 HOURS LATER: EFFECT OF METYRAPONE. **Schaefer, T.L.**; Williams, M.T.; Ehrman, L.A.; Gudelsky, G.A.; Vorhees, C.V.

11:45 TRANSPLANTED STROKE ANIMALS DISPLAY NORMALIZED CEREBRAL BLOOD FLOW AND BBB PERMEABILITY DURING ONSET OF BEHAVIORAL RECOVERY. Lind, J; Cheng, C; Hadman, M; Goodman, D; Chopp, M; **Borlongan, CV.**

12:00 **Adjourn**

1:00-5:00 **Group Excursion** – Rain Forest Tour and Luquillo Beach (Registration separate – cost \$40)

Wednesday, April 23

5:30-6:00 Marjorie A. Myers Lifetime Achievement Award in Behavioral Neuroscience: Joseph P. Huston

NEURONAL HISTAMINE: THE NEGLECTED NEUROTRANSMITTER AND ITS FUNCTIONS. Huston, J.P. Institute of Physiological Psychology, University of Düsseldorf, Düsseldorf, Germany. Neuronal histamine has an anatomical focus of neurons in the posterior hypothalamus and widespread projections throughout the brain, and thus has an organization comparable to that of the well known conventional neurotransmitters DA, NE, 5-HT and ACh. I will summarize recent advances in understanding the functions of this neglected neurotransmitter, with emphasis on its role in sleep/wakefulness, feeding, reinforcement and memory processes.

6:00-7:00 Keynote Speaker: Jeffrey Gray

IMPLICATIONS OF SYNESTHESIA FOR FUNCTIONALISM: THEORY AND EXPERIMENTS. Gray, J.A. Dept. of Psychology, London, SE5 8AF UK. Functionalism offers an account of the relations that hold between behavioural functions, information and neural processing, and conscious experience from which one can draw two inferences: (1) for any discriminable difference between qualia there must be an equivalent discriminable difference in function; and (2) for any discriminable functional difference within a behavioural domain associated with qualia, there must be a discriminable difference between qualia. The phenomenon of coloured hearing synaesthesia (in which individuals see colours when they hear or see words) appears to contradict the second of these inferences. I report data from behavioral and fMRI experiments showing that this form of synaesthesia is genuine and probably results from an aberrant projection from cortical language areas to a region (V4/V8) specialised for the perception of colour. Since functionalism purports to be a general account of consciousness, one such negative instance, if it can be further sustained empirically, is sufficient to invalidate it.

Thursday, April 24

8:00-10:00 Symposium 1: Prenatal cocaine and attentional processes: Evidence for teratogenic effects on developing catecholamine systems.

LASTING EFFECTS OF PRENATAL COCAINE EXPOSURE ON SUSTAINED AND SELECTIVE ATTENTION AND REACTIVITY TO ERRORS. Strupp BJ; Gendle MH; Morgan RE; Garavan H; White TL; Strawderman MS; Mactutus CF; Booze RM; Levitsky DA. Cornell Univ., Ithaca, NY 14853, & Univ. of South Carolina, Columbia, SC 29208. This talk will describe the emerging profile that characterizes rats exposed to cocaine prenatally via the IV route, at doses that model recreational use. The effects are very selective, reflecting deficits in 2 specific domains: attention and reactivity to errors. This talk will focus on the effects observed in 3 tasks: (1) an extradimensional shift (EDS) task in which the predictive dimension shifted between spatial & olfactory cues; (2) a sustained attention task in which the onset time, location, & duration of a brief visual cue varied randomly across trials; & (3) a selective attention task, similar to the previous task but including the presentation of an olfactory distracter on some trials. Perhaps most prominently, attention in the cocaine-exposed animals seemed to be "captured" by the most salient cues in the environment, resulting in greater distractibility when potent distractors were presented in the visual attention task, as well as slower learning in the EDS task when the less salient cues were predictive. This impairment in selective attention was seen in both sexes, at all three cocaine doses (0.5, 1.0, and 3.0 mg/kg). The ability to sustain attention was also impaired, but this effect was only seen in the highest cocaine exposure group and was more pronounced in the males. Finally, the disruptive effect of committing an error was more pronounced in the cocaine-exposed males than in controls, an effect that may reflect an impaired ability to regulate emotions or stress. Supported by NIDA grants DA 07559, DA 09160, DA1137 & F31DA14448-01A1

DOPAMINERGIC NEUROTRANSMISSION FOLLOWING PRENATAL IV COCAINE EXPOSURE. Booze, RM; Hasselrot, U.; Salvatore, MF; Hudspeth, O; Gerhardt, GA; Strupp, BJ; Snow, DM; Welch, MA; Mactutus, CF. The emerging profile of prenatal cocaine exposure presents two prominent features in the offspring: cognitive/attention deficits and motor/tone abnormalities. One candidate mechanism, long-lasting alterations in dopaminergic neurotransmission, has not been systematically investigated in a clinically relevant rodent model. Long-Evans female rats were implanted with an IV access port, bred, and given saline or cocaine-HCl (3 mg/kg/ml) for gestational days (GD) 8-14 (1x/day), GD 15-21 (2x/day), or GD 8-21 (1x/day-GD 8-14, 2x/day-GD 15-21). Densities of D1, D2, and D3 receptors, as well as the dopamine transporter (DAT) were determined with autoradiography in offspring at 270 days of age. D1 receptor density was decreased 25% in striatum (STR) and 35%

in nucleus accumbens (NAC) in GD8-21 exposed males. D3 receptor density was decreased 43% in ventral striatum (vSTR) and 53% in NAC in GD15-21 exposed females. D2 and DAT values were unchanged. High-speed in vivo chronoamperometric recordings were used to measure potassium-stimulated DA release and clearance properties in STR and NAC core of male offspring 90-150 days after birth. Evoked DA signal amplitudes in prenatal cocaine-exposed groups were 50-70% greater than that of the saline group in STR as well as the NAC core. In offspring exposed to cocaine at GD 8-21, the time required to clear 80% of the evoked DA signal (T80) in STR at DA concentrations between 2.2 and 3.8 μ M was significantly increased (nearly 3-fold) and the clearance rate of DA was nearly half of that in the control group. Clearance time of evoked-DA in the NAC was also significantly increased in the animals exposed at GD 8-21. Thus, using physiologically relevant levels of maternal cocaine exposure, long-lasting effects were noted on DA neurotransmission in the motor and reward centers of the CNS, resulting in a hyperdopaminergic state that may underlie the prominent abnormalities of in utero cocaine exposed offspring. Supported by DA11337, DA09160, DA14944 DA014401, DA013965 & DA12719.

EARLY PRENATAL COCAINE AND TERATOGENIC EFFECTS ON THE LC AS REVEALED IN BEHAVIOR AND ANATOMY. Mactutus, CF; Hasselrot, U; Strupp, BJ; Snow, DM; Welch, MA; Booze, RM. Given that prenatal COC exposed infants display alterations in brainstem auditory evoked responses as well as consistent alterations in attentional processes, deficits in the pre-attentive process of sensory gating may provide a most parsimonious explanation of the attentional deficits. We determined whether prenatal IV COC alters the preattentive process of sensory gating, as indexed by prepulse inhibition (PPI) of the auditory startle response (ASR), and whether this effect varied as a function of gestation exposure period. Long-Evans female rats (N=64) implanted with an IV access port, were bred and given saline or COC HCl (3 mg/kg/ml) from GD8-14 (1x/day), GD15-21 (2x/day), or GD8-21 (1x/day-GD8-14, 2x/day-GD15-21). At 100 days of age, the most prominent effect of prenatal COC was a sex-dependent shift in ISI for maximal inhibition for GD8-14 animals, and a sex-dependent flattening of the peak inhibition curve for the GD8-21 and GD14-21 animals. At 120 days of age, idazoxan (an α -2 antagonist, 0.5 mg/kg) differentially increased the magnitude of the ASR on control trials (SAL, 72.0% > COC GD8-21 > COC GD15-21 > COC GD8-14, 19.3%) and differentially affected response latency as a function of prenatal COC and ISI (COC GD8-14 > SAL at 8 msec, but < at 80 msec ISI). At 270+ days of age, apomorphine (APO: 0-0.5 mg/kg/ml), preferentially decreased response magnitude ~60% for GD15-21 animals (~30% for all other groups). Flattening of the response latency by ISI function after APO was most pronounced in the COC GD15-21 group, but not COC GD8-14 group. Unbiased cell counting of LC neurons in another cohort of animals at 21 days of age indicated a sex-dependent loss of neurons following GD8-14 cocaine exposure. In sum, the preattentive processes of sensory gating is adversely affected by prenatal COC exposure, and further, prenatal COC appears to differentially affect neurogenesis of the noradrenergic and dopaminergic systems, dependent upon gestational timing of exposure. Supported by DA11337, DA09160, DA014401, DA013965 & DA12719.

PRENATAL COCAINE EXPOSURE COMPROMISES OUTGROWTH POTENTIAL IN DEVELOPING LOCUS COERULEUS NEURONS. Snow, D.; Carman, H.; Smith, J.; Welch, M.; Booze, R.; Mactutus, C. University of Kentucky, Lexington, KY 40536; University of South Carolina, SC 29208. Cocaine use during pregnancy is associated with neurobehavioral problems in school-aged children that implicate alterations in attentional processing, possibly due to impairments in the noradrenergic (NE) system. We analyzed locus coeruleus (LC) neurite outgrowth characteristics: 1) following the administration of a physiologically relevant concentration (16 nM) of cocaine in tissue culture, 2) following dosing using a clinically relevant model for fetal cocaine exposure from GD8-21 (3 mg/kg/ml, 1x/day-GD8-14 and 2x/day-GD15-21) prior to cell culture, and 3) following in utero cocaine exposure either early (GD8-14), late (GD15-21), both early and late, or neither (control) prior to cell culture. Results showed that cocaine induced a decrease in cell adhesion ($P < 0.0001$) and a decrease in the number of cells with neurites ($P < 0.001$). Morphological differences between neuronal cultures treated with cocaine and non-treated controls were also readily apparent. When comparing equal cell densities, early gestational exposure to cocaine inhibited LC neurite outgrowth (reduced total neurite length, $p < 0.0005$; reduced neurite length per cell, $p < 0.0033$), and moreover, early gestational cocaine exposure of LC neurons inhibited neurite outgrowth in female offspring greater than in male offspring (reduced total neurite length and neurite length/cell, $p < 0.0001$). These converging data are significant in that they: 1) demonstrate a direct disruptive effect of cocaine on NE neurons of the LC, 2) provide a neurobiological basis for the alterations in the offsprings' attentional processes consequent to in utero cocaine exposure, and 3) provide a model to elucidate the mechanisms by which cocaine affects neuronal development. [Support DA12719 (DMS), DA11337 and DA014401 (RMB), DA09160 (CFM)].

10:30-12:00 Oral Session 1: Stress and Anxiety.

SEX-SPECIFIC BEHAVIORAL EFFECTS OF ANABOLIC STEROIDS IN MICE. Barreto-Estrada, J.; Barreto, J.; Fortis, A.; Fortis, Y.; Rojas, Y.; Corretjer, G.; Jorge, J.C. Dept. of Anatomy, Medical Sciences Campus, University of Puerto Rico 00936. Anabolic androgenic steroids (AAS) have become a major class of drugs of abuse despite the detrimental effects on endocrine function and affect. AAS can act as allosteric modulators of the GABA receptor. In

this study, we investigated the behavioral effects of AAS in locomotor-, aggressive-, anxiety-, social-, and sexual-behaviors in adult mice (C57Bl/6) from both sexes. Sustained exposure to AAS was achieved via a subcutaneous implant filled with 17 α -methyltestosterone (7.5 mg/kg). After 14 days, a significant decrease in ovarian ($p < 0.05$) and testicular ($p < 0.005$) weight was observed, while body weight was not altered. AAS exposed-females displayed irregular estrous cyclicity as over 60% of these females were locked in estrous. A battery of behavioral tasks revealed that: 1) changes in social interaction were sex-specific, females showed an increase in mounting behavior and grooming where males displayed and increase in body contacts, 2) AAS-exposed males, but not females, were less defensive than control animals ($P < 0.05$), 3) most locomotor and exploratory behaviors were not affected by AAS treatment, 4) risk assessment behaviors in the Elevated Plus Maze (EPM) were affected in males, but not females, even though other EPM parameters were unaltered, 5) the Vogel Conflict Test revealed an anxiolytic response in males, but not females, as observed in the recovery time after punishment ($p < 0.05$). Taken together, we have found that chronic exposure to AAS affects endocrine function and behavior according to sex in C57Bl/6 mice. We aim to determine the involvement of the GABAergic system of these behavioral responses. Supported by NIH-BRIN (RR16470).

AVERSION AND CONDITIONING: THE CASE OF PREDATOR ODORS. Blanchard DC; Markham C; Yang M; Hubbard D; Blanchard RJ. Low levels (0.01, 0.05, and 0.1 μ l) of trimethylthiazoline (TMT), a derivative of fox feces, produce significant changes in defensiveness in rats on exposure, but this exposure does not later result in a significant change in behavior to context/cue stimuli alone (conditioning). When cat urine, cat feces, and cat fur/skin odor were used in the same test, both feces and fur/skin odors elicited virtually identical patterns of change in defensive behaviors during exposure, but only the fur/skin odor group showed significant conditioning to the exposure cue + context. Results suggest that avoidance of a stimulus is not closely associated with the development of aversive conditioning to that stimulus, a conclusion that is consonant with analyses of the results of a number of drug effects on defensive behaviors in a test battery including flight and a measure of residual emotionality/context conditioning. While aversive conditioning does appear to be linked to risk assessment and defensive threat/attack effects of drugs, it is much less closely linked to the effects of drugs on flight/avoidance measures.

THE RAT EXPOSURE MODEL: A NOVEL MODEL OF RISK ASSESSMENT, AVOIDANCE, AND FREEZING FOR MICE. Blanchard, R.J.; Yang, M.; Augustsson, H.; Blanchard, D.C. Mice in an apparatus containing a chamber connected via a tunnel to a partitioned cage separating the mouse from an active predator (rat), show marked elevations of a number of defensive behaviors, compared to toy-rat exposed controls. C57BL mice showed higher levels of avoidance, freezing, risk assessment, and defensive burying (shoveling the chamber bedding into the tunnel) than BALB/c, Swiss-Webster and CD-1 strains. Congruent with reports that BALB/c mice fail to tunnel in seminatural environments, these animals showed no defensive burying. Chlordiazepoxide (2.5, 5.0, and 10.0 mg/kg) reduced both risk assessment and avoidance at non sedative doses, but increased freezing. These data support previous findings of a link between risk assessment and anxiolytic action, and suggest that the high risk assessment baseline of the Rat Exposure model may provide a sensitive behavioral assay for analysis of behavioral and pharmacological mechanisms in anxiety.

AGGRESSIVE BEHAVIOR AND UNPREDICTABLE CHRONIC MILD STRESS IN MICE: INTERACTIONS AND LIMITATIONS. Mineur Y.S.; Prasol D.J.; Belzung C.*; Crusio W.E. Brudnick Neuropsychiatric Research Institute, 303 Belmont Street, Worcester, MA 01604 USA; *Psychobiologie des Emotions, UFR Sciences et Techniques, Tours France. A significant proportion of patients suffering from major clinical depression exhibit sudden bursts of anger referred to as "panic attacks without anxiety or fear". So far, only few studies have examined aggressive behaviors in rodent models of depression, and results have been inconclusive. Furthermore, some of the approaches used are of limited use only, because they involve only a narrow portion of what can lead to depressive behavior and depression-related aggression (single gene targeting for instance). We investigated aggressive behavior in mice from three different inbred strains subjected to unpredictable chronic mild stress (UCMS). Our results corroborate previous studies demonstrating that UCMS induces a depressive-like state (as evidenced by decreased grooming, state of passivity, increased anxiety), with severity of symptoms differing according to the genetic backgrounds. We showed that UCMS increased aggression in a strain-dependent manner. These results demonstrate that the UCMS model may provide a valuable tool to investigate genotype*environment interactions involved in the development of a depressive state and associated phenotypes.

CENTRAL ADMINISTRATION OF A NEUROSTEROID INTO THE BASOLATERAL AMYGDALA MODIFIES ANXIETY IN AN ESTROGEN-DEPENDENT MANNER. Pérez-Acevedo, N.L.¹; García E.²; Jorge J.C.¹ Department of Anatomy¹, Medical Sciences Campus, Department of Chemistry², Río Piedras Campus, University of Puerto Rico, San Juan, P.R. 00936. The goal of this study is to investigate the modulatory roles of the endogenous testosterone metabolite 5 α -androstane-3 α , 17 β -diol (3 α -DIOL) on affective components of behavior when infused into the basolateral amygdala [(AMY-bla), coordinates from bregma, AP -2.80, DV 5.0, 2mm above the AMY-bla] of the amygdala complex. Ovariectomized (OVX) adult female rats, half receiving empty implants

and half receiving implants containing estradiol benzoate (OVX-EB) were employed (n=32). Three different approaches were used to study the role of the neurosteroid 3 α -DIOL on anxiety and reward when microinjected either with 3 α -DIOL (10⁻⁶ M) or vehicle (0.5 μ l/min/side): the Elevated Plus-Maze (EPM), the Vogel Conflict Test (VCT) and the Conditioned Place Preference (CPP). Analysis of anxiety-related behaviors showed that central infusion of 3 α -DIOL into the AMY-bla in OVX-EB animals, produces anxiolytic effects ($p \leq 0.05$) whereas OVX animals showed a tendency toward anxiogenic responses. These results are quite provocative. We hypothesize that androgens not only act through conventional mechanisms (genomic mechanism) but through membrane-bound receptors (non-genomic mechanism) by modulating GABA_A receptors in a non-endocrine region such as the AMY-bla to modify affect according to the endocrine state of the animal. Study supported by NIH-COBRE (RR15565) to JCJ.

NEUROENDOCRINE DEVELOPMENT OF RHESUS MACAQUE INFANTS DURING THEIR FIRST TWO YEARS OF LIFE: EFFECTS OF SEX AND EARLY EXPERIENCE. Maestriperi, D. Institute for Mind and Biology, The University of Chicago, Chicago, IL 60637 USA. The effects of early abuse on HPA axis activity under basal and challenge conditions were evaluated in group-living rhesus macaque infants during their first two years of life (at 5, 10, 17, and 22 months of age). Ten infants (4 male, 6 female) who were physically abused by their mothers and 10 age-matched nonabused controls (4 male, 6 female) served as study subjects. Basal plasma cortisol levels increased steadily with age in all male and female infants. Abused infants tended to have lower basal cortisol than controls. All infants responded with similarly elevated plasma cortisol to stress without any effects of sex or early experience. Females showed higher cortisol responses to a CRH challenge than males did at all ages. There was also an interaction between sex and early experience such that the cortisol elevations in response to the CRH challenge were higher for abused than control females whereas the opposite was true for males. In the first year of life, but not in the second, abused infants showed hypersuppression of cortisol in response to a dexamethasone challenge relative to controls. These findings are discussed in relation to current knowledge of HPA axis development in primates and research on post-traumatic stress disorder.

2:00-3:00 Presidential Address: Mark A. Geyer.

3:15-5:35 Student Travel Award Blitz - Abstracts in poster section.

6:00-8:00 Poster Session I: Topics: Modeling Neurodegenerative and Psychiatric Disorders, Learning and Memory, Drugs of Abuse, Attention, Education.

1. GD3 SYNTHASE KNOCKOUT MICE ARE RESISTANT TO β -AMYLOID BINDING AND β -AMYLOID-INDUCED NEUROTOXICITY. Olaghere-DaSilva, Uade; Bernardo, Alexandra; Zhao, Jiali; Hipkens, Susan; Bruchey, Aleksandra; McDonald, Mike. β -amyloid (A β) is a fibrous protein that aggregates into plaques in the brains of Alzheimer's patients. Recent studies have shown that gangliosides, glycolipids richly expressed in neuronal membranes, are necessary for A β binding and aggregation in vesicle preparations. In addition, the ganglioside GD3 has been shown to be necessary for certain types of cell death, including A β -induced apoptosis. Knocking out the GD3 synthase (GD3S) gene effectively eliminates half of the major brain gangliosides including GD3. The present study examined the effect of this manipulation on learning and memory, and the susceptibility of GD3S^{-/-} neurons to A β binding and A β -induced toxicity, using a battery of behavioral tests designed to detect differences in learning and especially memory. Our results thus far show that the GD3S knockout mice are behaviorally normal. Cultured primary cortical neurons from GD3S^{-/-} mice show a gene-dose-dependent reduction in exogenous A β binding, and a resistance to A β -induced toxicity.

2. FOLATE DEFICIENCY INDUCES HIPPOCAMPAL CELL DEATH AND EXACERBATES MEMORY DEFICITS IN APP TRANSGENIC MICE FOLATE DEFICIENCY INDUCES HIPPOCAMPAL CELL DEATH AND EXACERBATES MEMORY DEFICITS IN APP TRANSGENIC MICE. Bernardo Alexandra, Olaghere-DaSilva Uade, Zhao Jiali, Hipkens Susan, McDonald Mike. The β -amyloid precursor protein (APP) over-expressing mouse (Tg2576) is a model of the β -amyloid (A β) aggregation and plaque formation of Alzheimer's disease. Previous studies have shown that these mice do not demonstrate cell death compared to their wild type littermates, which is an important feature of Alzheimer's disease. Recent studies have demonstrated that diets deficient in folic acid and containing increased levels of homocysteine can sensitize hippocampal neurons to A β -induced toxicity. Three months of this experimental diet induces hippocampal cell death in APP transgenics but not in wild-type controls. We are interested in whether this increase in toxicity will also increase the memory deficits of APP transgenic mice, and lead to greater plaque formation. Twenty-two animals were divided into two groups. One group was fed a diet that was deficient in folic acid with increased levels of homocysteine. The control group was fed a standard mouse diet with defined levels of folic acid and choline and lacking homocysteine. Animals were fed the diets for a period of 3 months and were tested on a battery of memory tasks. Preliminary results from indicate that

the folate deficient diet produced further deficits in performance in APP transgenic mice.

3. DEPRESSION IN A GROUP OF PUERTO RICAN WOMEN WITH PARKINSON'S DISEASE. Pita, I.; Serrano, C.; Wojna, V. Neurology Section, University of Puerto Rico. The purpose of this study is to correlate depression, dementia and disease severity in a group of Puerto Rican women with Parkinson's Disease (PD). Background: Neuropsychiatric disorders, including depression and dementia, have been frequently described in PD. Depression has been reported from 35 to 50% on PD patients, with higher incidence in women. Dementia has been reported in up to 30% of PD patients. Methods: A cross-sectional study was performed. History included age and years with PD. Screening tests used included CES-D for depression and Mini-mental scale (MMS) for dementia. PD staging, (Hoehn and Yahr (H&Y) scale), was obtained by an examiner blind to patient's history. Results: 14 Puerto Rican female patients (mean age 64.8) with PD were recruited. 57.1% (8) had a CES-D consistent with depression (>18). 28.5% (4) had MMS consistent with cognitive impairment (≤ 23). All women with depression had low H&Y (≤ 3 , indicative of mild motor deficit), when compared to the non-depressed women who had H&Y >3 (severe deficit). Cognitive impairment was evident in 1 woman with depression and in 3 non-depressed women. Women with PD for ≤ 10 years presented with depression more frequently than women with PD for >10 years. Younger women (mean 60 years) had depression more frequently than older women (mean 70). Conclusion: In our study mild to moderate PD and less years with PD correlated with an increase frequency of depression whereas advanced PD correlated with decrease frequency of depression. Advanced disease correlated with increase frequency of cognitive impairment, which could account for the lesser frequency of depression. This study suggests a trend for an increase frequency of depression at early stages of PD and in younger women.

4. IMPLICIT LEARNING IN AN ANIMAL MODEL OF HUNTINGTON'S DISEASE. Jay, J.R.D.; Dunnett, S.B. Brain Repair Group, Cardiff University. Cardiff, CF10 3US, UK. Corticostriatal pathways are believed to underlie implicit motor learning, and patients with Huntington's disease (HD), a progressive neurodegenerative disease of the striatum, are impaired in motoric forms of implicit learning (IL). Animal correlates of HD-like IL deficits have, to our knowledge, never been tested. Disruption and subsequent graft-derived restoration of IL in an animal model of striatal degeneration will enrich our understanding of IL in animals and enhance the profile of graft-derived recovery in patients with HD. To establish and characterize IL, we created a modified 5-choice serial reaction time task for use in 9-hole-array operant testing chambers. 40 adult female Sprague-Dawley rats were trained to make consecutive responses to two of five possible response locations in order to receive a sucrose reward. Each trial consisted of two consecutive stimuli, with three of the five primary stimuli preceding random secondary stimuli (random trials), and two of the five primary stimuli always preceding fixed secondary stimuli (fixed trials). Implicit learning, as measured by decreased reaction time in fixed trials, should be sensitive to medial but not lateral striatal lesions. After receiving bilateral excitotoxic or sham medial or lateral striatal lesions, rats will be reassessed on IL. To clarify the nature and stability of post-lesion deficits, task complexity will be altered by reducing the duration of individual stimuli, by shortening the delays between primary and secondary stimuli, and ultimately by shifting the paired stimuli to assess interference and to probe acquisition of implicit sequences after striatal disruption. Work supported by the Marshall Commission.

5. DISTINCTIVE BEHAVIORAL PROFILES IN ANIMAL MODELS OF PARKINSON'S DISEASE, STROKE, AND TRAUMATIC BRAIN INJURY. Woodlee, MT; Fleming, SM; Schallert, T. Forelimb sensorimotor function was assessed in rat models of Parkinson's disease, focal cortical ischemia, and traumatic brain injury using a novel variant of the vibrissae-elicited forelimb placing test which involves testing across the midline. In addition to traditional "same-side" placing tests, rats were held on their sides to stimulate the vibrissae contralateral to the forelimb in which placing was being evaluated. Also, midline stimulation of the chin was tested for its effect on placing. Using these variants of the placing test, distinctly different patterns and time courses of recovery were noted for the various types of brain injury examined. In addition, long-term chronic deficits markedly differed between injury types, and appeared to be related to the type of striatal damage that was sustained. The possible relationships between these effects and anatomical events associated with functional recovery are discussed, as are treatment effects. In particular, a striking neuroprotective effect of methylphenidate administration against 6-OHDA induced striatal neurotoxicity was noted, and data from the aforementioned placing test will be presented which demonstrate a long-term behavioral protective effect associated with this treatment.

6. INTRACELLULAR SIGNALING PATHWAYS IN BIPOLAR DISORDER Einat, H.; Yuan, P.X.; Chen, G.; Dogra, S.; Manji, H.K. Lab. Molec. Pathophysiology, NIMH, NIH, DHHS. Background: The complexity of bipolar disorder (BD) has hindered our ability to identify the pathophysiology of this devastating disorder. In recent years, focus of research in BD has shifted from biogenic amines to intracellular 2nd messenger systems. In this context, studies in postmortem human and rodent brain tissue suggests that 2 major signaling pathways – the PKC & ERK MAP kinase pathways may be involved in the pathophysiology & treatment of BD. To date, however, there have been no behavioral studies to establish a clear link between biochemistry and clinical symptoms. Methods: We have therefore undertaken a series of rodent behavioral studies to establish the involvement of the ERK & PKC signaling

pathways in affective-like behavior. Results: Several novel findings have emerged: (i) ERK inhibition reduces immobility in the Forced Swim Test & increases activity in a large open field, effects that are normalized by chronic lithium; these changes resemble a manic-like state (ii) PKC inhibition reduces amphetamine-induced behavior in a large open field without affecting spontaneous activity levels & abolishes the expression of amphetamine-induced sensitized behavior. These changes strikingly resemble the effects of mood stabilizers. Concomitant biochemical analysis shows that the behavioral effects are accompanied by discrete changes in the ERK and PKC signaling pathways in relevant brain areas. Conclusions: Our results support previous molecular studies, and suggest that both ERK & PKC signaling may play important roles in distinct facets of BD. More importantly, these studies establish the feasibility of using combined biochemical/behavioral strategies to study intracellular pathways.

7. IMPULSIVITY AND IMPAIRED ATTENTION IN A MOUSE MODEL OF ATTENTION DEFICIT HYPERACTIVITY DISORDER Miller, L.R.; Siesser, W.B.; McDonald, M.P. Center for Molecular Neuroscience, John F. Kennedy Center. Vanderbilt University, Nashville, TN 37232 USA. Impulsive behavior, inattentiveness, and hyperactivity are primary features of attention deficit hyperactivity disorder (ADHD). Resistance to thyroid hormone (RTH) is a human syndrome linked to a mutation of the ligand binding domain on the thyroid receptor β gene (TR β). The syndrome is characterized by reduced tissue responsiveness to thyroid hormone and elevated serum levels of thyroid hormones. In addition, 50% to 70% of all RTH patients have been diagnosed with ADHD. Our lab works with a transgenic mouse expressing a mutant TR β gene derived from a patient with RTH and ADHD. Previous studies have shown that the TR β transgenic mice have a transient deficit on the simple reaction time task when the reinforcer is degraded. In order to test for deficits in sustained attention, the TR β transgenic mice and wildtype controls were trained on the serial reaction time task using varying schedules of reinforcement and durations of the cue light. Impulsivity was measured using the delay of gratification procedure, in which subjects had repeated choices between a large reinforcer delivered after a delay (0,4,8,16,or 32s) and a small reinforcer delivered immediately. Future studies will test the effects of methylphenidate on the performance of the TR β transgenic mice on these tasks.

8. ABNORMAL ATTENTION AND MOTIVATION IN A MOUSE MODEL OF RESISTANCE TO THYROID HORMONE. Siesser, W.B.¹; Cheng, S.-Y.²; McDonald, M.P.¹ 1. Center for Molecular Neuroscience, John F. Kennedy Center. Vanderbilt University, Nashville, TN 37232 USA. 2. Gene Regulation Section, National Cancer Institute, Bethesda, MD USA. Impulsive behavior, inattentiveness, and hyperactivity are primary features of attention deficit hyperactivity disorder (ADHD). Resistance to thyroid hormone (RTH) is a human syndrome linked to a mutation of the ligand binding domain on the thyroid receptor β gene (TR β). The syndrome is characterized by reduced tissue responsiveness to thyroid hormone and elevated serum levels of thyroid hormones. In addition, 50% to 70% of all RTH patients have been diagnosed with ADHD. Our lab works with a transgenic mouse expressing a mutant TR β gene derived from a patient with RTH and ADHD. Previous studies have shown that the TR β transgenic mice have a transient deficit on the simple reaction time task when the reinforcer is degraded. In order to test for deficits in sustained attention, the TR β transgenic mice and wildtype controls were trained on the serial reaction time task using varying schedules of reinforcement and durations of the cue light. Impulsivity was measured using the delay of gratification procedure, in which subjects had repeated choices between a large reinforcer delivered after a delay (0,4,8,16,or 32s) and a small reinforcer delivered immediately. Future studies will test the effects of methylphenidate on the performance of the TR β transgenic mice on these tasks.

9. BEHAVIOR, BRAIN METABOLISM AND D1 RECEPTOR EXPRESSION CHANGES FOLLOWING REPEATED TREATMENT WITH METHYLPHENIDATE IN ADHD ANIMAL MODEL. Viggiano, D.(1); Vallone, D.(3); Ruocco, L.A.(1); Sadile, A.G.(2) 1 Inst. Human Anatomy & 2 Lab. Neurophysiol., Behav. & Neural Networks, Dept Exptl Med, SUN, Naples; 3 Max-Planck Institute für Entwicklungsbiologie, Friedrich Miescher Laboratorium, Tuebingen. A hyperfunctioning mesocorticolimbic (MCL) dopamine system may underlie Hyperactivity and Attention Deficit (ADHD) in an animal model. Psychostimulant drugs, such as methylphenidate (MP) have been used for over five decades for the treatment of ADHD, but their mechanism of action remains unclear. In this study we repeatedly treated hyperactive and normal control rats with MP and studied the effects on behavior, tyrosine hydroxylase (TH) and dopamine D1-receptor expression, and mapped changes in metabolic brain activity. The respiratory chain enzyme cytochrome oxidase (C.O.) has been used as a functional imaging probe to map enduring changes in brain activity induced by low MP doses. To this aim, male prepubertal NHE and control rats (NRB) received daily MP injections (3mg/kg i.p.) or vehicle for 15 days. A third group did not receive any injection (basal state). At the age of 40 days, animals were tested in a spatial novelty (Låt Maze) for 30min, two hours after last injection. The behavior was videotaped and off-line analyzed for indices of locomotor activity (traveled distance and number of rearings) and non-selective attention (scanning duration). Immediately after the test, brains were removed, quickly frozen and stored at -80° . They were either dissected to isolate mRNA from the prefrontal cortex and striatum for RNAase protection assay, or cryosectioned in fifty-micron thick coronal sections for C.O. histochemistry and TH immunohistochemistry. RNAase protection showed down-regulation of D1 receptors in the PFC of NHE rats that was reversed by MP. PC-assisted light microscope image analysis (MCID-M2)

showed a decreased CO activity in the medial prefrontal cortex in both NHE and NRB rats, and in the striatum only in NRB rats. Moreover, TH expression increased in the VTA of NHE rats. These findings indicate that (i) MP modulates neural activity at main target sites of the MCL system, (ii) low doses of MP decrease MCL activity probably via D-2 autoreceptors at somatodendritic synapses, (iii) a disintegration in the fronto-striato-pallido-thalamo-cortical system between frontal cortex and striatum. Thus, the differential psychostimulant effect might be due to genotype-dependent basal functional network operations. Supported by COFIN 2001

10. PRENATAL INHIBITION OF ENDOCANNABINOID REUPTAKE REDUCES ACTIVITY AND MODIFIES THE UNBALANCE BETWEEN MESOSTRIATAL AND MESOCORTICOLIMBIC DOPAMINE SYSTEMS IN THE NAPLES HIGH EXCITABILITY RATS. Viggiano, D. (1); Ruocco, L.A.; Pignatelli, M.; Sadile, A.G. Lab. Neurophysiol., Behav. & Neural Networks, Dept Exptl Med, & 1 Inst. Human Anatomy; SUN, Naples. Endogenous cannabinoids may exert a neurotrophic effect on developing mesencephalic dopamine neurons. An altered mesocorticolimbic system seems to underlie hyperactivity and attention deficit in clinical and animal studies of Attention Deficit Hyperactivity Disorder (ADHD). Therefore prenatal elevation of anandamide has been induced in Naples High Excitability (NHE) rats by inhibition of its reuptake. To this aim, pregnant NHE and random-bred females received a subcutaneous injection of AM404 (1mg/Kg) or vehicle daily from E11 until E20. Adult offsprings were exposed to a spatial novelty (Låt-maze) for 30 min. and the behavior was videotaped and off-line analysed for indices of activity (traveled distance, rearing frequency) and attention (scanning duration). Moreover, pot-hoc morphological analysis of the brains was carried out that pertained to metabolic activity by cytochrome oxydase and thyrosine hydroxylase as marker of the dopamine systems. The results indicate that prenatal AM404 treatment significantly reduces activity by about 20% during the entire testing period and modifies the distribution of scanning times towards episodes of shorter duration in the first part of the test only in NHE rats. In addition, image analysis revealed a significant increase in relative optical density of TH+ terminals in the dorsal striatum and substantia nigra of AM-404 treated NHE rats and minor changes in the dorsal cortex of AM-404 treated NRB rats. Data suggest a correction of the unbalance between the two dopamine systems by prenatal anadamide that leads to reduced hyperactivity and modified scanning times in this animal model of ADHD. This, in turn, might open new strategies in the treatment of a subset of ADHD cases. Supported by COFIN 2001 grant.

11. NOVEL MULTIPLE EXPERIENCE PARADIGM (MEP): A MODEL FOR NEUROPSYCHIATRIC DISEASE? Al Banchaabouchi, M.; Pereira, L.; Pagán, J.; Pérez, R.; Peña de Ortiz, S. Department of Biology, University of Puerto Rico, P.O. Box 23360 San Juan P.R. 00931. The etiology of neuropsychiatric diseases, such as schizophrenia, is multifactorial, including substantial contribution of genetic, neurodevelopmental, and environmental factors. We have developed a novel behavioral model termed the multiple experience paradigm (MEP) and are studying its impact on cognitive, emotional, and behavioral performance in mice. We also aim to establish molecular and genetic correlates associated with MEP behavior that may have relevance to schizophrenia. Male wild type C57J/B16 animals were used at age of weaning (3-4 weeks). Mice were divided in 3 groups: Naïve, MEP Positive, and MEP Negative. The MEP consisted of subjecting the animals to various "positive" or "negative" life-experiences spaced during a 3-week period. The animals were then subjected to a battery of behavioral tests including general locomotor activity, object recognition learning and memory, spatial discrimination learning, and fear conditioning. Our results support our hypothesis that negative life experiences early in life produce a behavioral phenotype that might associate to psychotic-like behavior. Specifically, while no differences were observed in object recognition and spatial discrimination learning and memory between the groups, the MEP negative group showed a significant impairment in contextual, but not cued, fear conditioning ($p < 0.05$, $N = 12$). Moreover, the MEP negative group displayed significantly more time performing stereotypic behaviors in an open field than the Naïve group ($p < 0.05$, $N=12$). Differences in nurr1 gene expression are being assessed in different brain regions to establish a molecular correlation between the behavioral effects observed and the mRNA and protein levels of a candidate gene for schizophrenia. This work is supported by SPO grant: NIGMS-MBRS SOGGMO 8102-26S and IDeA-COBRE: NCCR-NIH 5P20 RR15565-02.

12. HABENULAR LESIONS CAUSE COGNITIVE IMPAIRMENT IN RATS: IMPLICATIONS FOR SCHIZOPHRENIA. Lecourtier, L.; Neijt, H.; Kelly, P.H. Cognitive impairment is a well-known hallmark of schizophrenia. Pathology of the habenula has been hypothesized to be involved in the etiology of schizophrenia. We therefore examined here whether damage to the habenula in rats caused behavioral changes similar to those seen in schizophrenia. Bilateral electrolytic lesions of the habenula were made in male Sprague-Dawley rats. The behaviors examined were social interaction, prepulse inhibition (PPI) of an acoustic startle response as an index of sensory gating and cognitive performance in the Morris water maze spatial memory task. The lesion size was verified by both histological staining and neurochemical assay of choline acetyltransferase in the interpeduncular nucleus, the terminal region of the habenulo-interpeduncular tract. Clear-cut impairment of Morris maze performance (latency and distance swum before finding the hidden platform) was observed. There were no significant changes in social interaction time and PPI. The results are consistent with the view that pathology of the habenula may indeed

contribute to the cognitive impairments of schizophrenia.

13. VALIDATION OF MICROARRAY DATA AND DETERMINATION OF SPECIFIC HIPPOCAMPAL SUBREGIONS INVOLVED IN LONG-TERM MEMORY BY LASER CAPTURE MICRODISSECTION AND QUANTITATIVE REAL TIME PCR. P.E. Vivas-Mejía, Y. Robles, J. Felix, H.G. Ortiz-Zuazaga and S. Peña de Ortiz*. Center for Molecular, Developmental, and Behavioral Neuroscience. Department of Biology, University of Puerto Rico, Rio Piedras Campus 3102, P.O. Box 23346, San Juan, PR 00931. Formation of long-term memory requires new gene transcription, yet information on learning associated genetic regulatory events is limited. We are using cDNA microarrays to profile hippocampal gene expression in spatial learning. For our initial studies adult male rats were separated into Naïve and Spatially trained groups. The results identified 19 genes showing significant differences in expression. Northern blots and in situ hybridization were used to validate hippocampal changes in expression for the delta opioid receptor 1. For additional validation studies animals were separated into Naïve, Pseudotrained, and Spatially Trained groups. After brain sectioning, we used Laser Capture Microdissection to obtain pure cell populations from the dentate gyrus, CA1, and CA3 subregions of the hippocampus. Following RNA extraction and reverse transcription we performed quantitative real-time PCR using SYBR green I, for additional candidate genes identified by our array studies. So far, we have confirmed the spatial learning specific hippocampal induction of the genes encoding protein kinase B and cell adhesion kinase beta. Interestingly, our studies also show regional specificity of spatial learning induced gene expression within the hippocampus that is particular to each gene studied. The results show that hippocampal gene expression is regulated in a gene and subregion specific fashion during acquisition of spatial discrimination learning. This work was supported by NIH (S.P.O. grants NIGMS-MBRS SOGGMO 8102-26S1, NINDS-SNRP U54 NS39405, and NCRR-NIH 5P20 RR15565-02).

14. THE DNA LIGASE INHIBITOR ARA-CTP BLOCKS LONG-TERM MEMORY OF CONDITIONED TASTE AVERSION. Wang, J.; Ren K.; Ramos, X.; Pérez, J.; Flores, G.; Pagán, J.; Peña de Ortiz, S. Department of Biology, University of Puerto Rico, P.O. Box 23360, San Juan, P.R. 00931-3360. We examined the hypothesis that DNA ligase-dependent recombination/repair processes are involved in learning and memory processes in the brain. Rats received intracerebroventricular infusions of the DNA ligase inhibitor 1-beta-D-arabinofuranosylcytosine triphosphate (ara-CTP) 30 min prior to conditioned taste aversion (CTA) training. While control and drug-treated animals showed similar patterns of total liquid ingestion at all time points tested, ara-CTP caused a significant blockade of CTA long-term memory (LTM) measured at 24 and 72 h after training. Short term memory measured 1 h after training was not affected by ara-CTP. Similar results were obtained with the protein synthesis inhibitor anisomycin. Animals in the ara-CTP and vehicle groups were subjected to a second CTA experience without additional drug infusions. The rats previously treated with ara-CTP could learn and remember the new CTA experience showing that the learning and memory circuits involved in CTA remained intact after the infusion of the drug. In experiments injecting ara-CTP 1 hr after CTA training we found no effect by the drug showing that in order to block learning and memory the drug must be present at the time of training. In accordance with these overall results, infusing ara-CTP directly into the CA1 region of the hippocampus prior to spatial training exerted a significant effect on long-term memory measured 7 days after acquisition. Finally, ara-CTP had no effect on affect in vitro transcription, while the drug effectively blocked non-homologous DNA end joining (NHEJ) activity of brain protein extracts. We suggest that DNA ligase-mediated DNA recombination/repair processes are necessary for the expression of LTM in the brain and that interfering with such processes affects future behavioral plasticity. This work was supported by NIH (S.P.O. grants NINDS-SNRP U54 NS39405, and NCRR-NIH 5P20 RR15565-02).

15. MECHANISMS OF LEAD-MEDIATED COGNITIVE IMPAIRMENT IN THE ADULT RAT BRAIN. Vázquez, A.; Peña de Ortiz, S. Biology Department, University of Puerto Rico, San Juan, Puerto Rico, Box 23360, 00931-23360. Lead (Pb+2) is a contaminant that is widely distributed in the environment. Exposure to Pb+2 results in cognitive and behavioral dysfunctions in the developing and the adult brain. A number of reports suggest that at least part of the effects of Pb+2 are due to its interference with normal Ca+2 signaling in neurons. The overall goal of this research is to define the molecular mechanisms by which Pb+2 interferes with cognitive processes in adult animals. The results reported here demonstrate that lead interferes with long-term memory (LTM) processes in the adult brain, while short-term memory is mostly unaffected in a spatial discrimination hippocampal-dependent task. Also, our data showed that Pb+2 interferes with the membrane translocation of Ca+2 and phospholipid dependent protein kinase C (PKC), which is known to be important in learning and memory processes. In addition, preliminary data showed that Pb+2 also interferes with the phosphorylation state of the mitogen activated protein kinase (MAPK) in cytosolic extracts of dorsal hippocampi. MAPK is known to activate CREB, a transcription factor that regulates the expression of genes required for LTM in the hippocampus. Thus we propose that Pb+2 does not interfere directly with PKC and that the Pb+2 memory impairment is the result of a generalized effect due to blockade of an upstream molecule in the cascade signaling events, which results in improper gene expression and protein synthesis. Since long-term memory requires changes in gene expression and new protein synthesis, we propose that the lead-induced impairment in LTM is due to an abnormal gene expression in the brain. Thus, the last objective will be aimed to generate hippocampal gene expression profiles for rats exposed to Pb+2 using the DNA

microarray technique. We expect that genes related to memory will be expressed in control but not in Pb+2 exposed rats. Moreover, this model of lead mediated neurotoxicity exposure will allow us to identify other important genes related to memory consolidation in the brain. This work was supported by NIH (S.P.O. grants NIGMS-MBRS SOGMO 8102-26S1, NINDS-SNRP U54 NS39405; and IDeA-COBRE: NCCR-NIH 5P20 RR15565-02) and the EPA (MAI STAR EPA Predoctoral Fellowship to A.V.).

16. MOLECULAR CHARACTERIZATION OF CREB IR TRANSGENIC SYSTEM IN MICE DURING MEMORY AND LEARNING PROCESSES. Chévere, I.; Wang, J.; Labault, J.; AJ Silva*, Peña de Ortiz, S. Department of Biology, University of Puerto Rico, P.O. Box 23360, San Juan, P.R. 00931-3360; *Department of Neurobiology, University of California, Box 951761, Los Angeles, CA 90095-1761 The cAMP-responsive element binding protein (CREB) is a transcription factor important for the establishment of long-term memory (LTM) processes. Recent studies showed, using an inducible CREB repressor (CREB IR) in a transgenic mice system, that CREB is required for both consolidation and reconsolidation of long-term memory in contextual and cued fear conditioning. Such studies also determined using cDNA microarrays that the 14-3-3-eta gene is induced in a CREB-dependent fashion 1 hour after contextual fear-conditioning training. In additional experiments, in situ hybridization analysis showed that the CREB-dependent induction of 14-3-3-eta after fear conditioning is localized to the lateral and basolateral amygdala. We are also examining the expression of 14-3-3-eta in wild type C57Bl6 mice after conditioned taste aversion training by in situ hybridization. Finally, we are examining the effects of CREB IR on hippocampal gene expression induced after object recognition and enriched environment training. Preliminary data with the object recognition paradigm suggests that CREB is required for long-term memory in this task. These studies will help define the molecular events that are downstream of CREB activation and that are necessary for long-term memory formation. This work was supported by NIH (S.P.O. and A.J.S. grant NINDS-SNRP U54 NS39405).

17. NEUROGRANIN ENHANCES THE HIPPOCAMPUS-DEPENDENT LEARNING AND MEMORY. Huang, F.L.; Wu, J.; Kolker, D.E.; Huang, K.P. NIH, Bethesda, MD 20892 USA Neurogranin (Ng), a PKC substrate and calmodulin (CaM)-binding protein, is expressed in brain regions that are important for learning and memory. Ng's binding of CaM is regulated by Ca²⁺ level, its phosphorylation by PKC and oxidation by NO. It has been suggested that neuronal Ng level regulates the free Ca²⁺ concentration and availability of Ca²⁺/CaM at any given level of Ca²⁺ influx. A strain of Ng knockout (KO) mice was generated to investigate the neural function of Ng. These mutant mice developed normally, however, compared to wild type (Wt) mice, they exhibited severe deficits in learning the spatial task as tested with Morris water maze and both contextual and cued fear conditioning. The performance scores of heterozygous (Het) mice were positively correlated to their individual hippocampal Ng level. High frequency stimulation (100 Hz) induced a higher potentiation in the CA1 region of hippocampal slices in Wt than those of Het and KO mice. The tetanus-frequency response curve of KO mice shifted to the right compared to that of Wt mice. These mutant mice also showed a lower level of activated CaMKII (50-60% of Wt). When subjected to fear conditioning or treated their hippocampal slices with NMDA, these mutant mice displayed reduced abilities to generate the autophosphorylated and activated CaMKII and PKCs, and phosphorylated and activated forms of MAP kinases and CREB, all of which are important signaling reactions that lead to long-term memory. These results implicate Ng, through its modulation of Ca²⁺ and Ca²⁺/CaM, in the enhancement of signaling pathways for learning and memory. In the Ng null mice, the neuronal signaling is greatly attenuated and the mice become learning disabled.

18. NUCLEOTIDE PHOSPHODIESTERASE INHIBITORS AND MEMORY IN THE RAT. Giorgi, M.(1); Modica A.(1); Pompili, A.(2); Pacitti, C.(2); Gasbarri, A.(2). (1)Department of Basic and Applied Biology; (2)Department of Sciences and Biomedical Technologies University of L'Aquila (Italy) The effects on memory impairment of cyclic nucleotide phosphodiesterase (PDE) inhibitors zaprinast, DC-TA 46 and rolipram were tested by means of Morris water maze; their ability to increase cyclic nucleotide levels in the hippocampus (HF) and striatum (CP) was also assayed. DC-TA 46 causes memory impairment at maximal dose of 20 mg/kg; lower doses reveal no such effect. Zaprinast proves to be effective at a 10 mg/kg dose, while rolipram is effective at 3 mg/kg and 30 mg/kg. Rolipram shows efficacy in raising cAMP concentration in the CP mainly at a 3mg/kg dose, while in the HF, doses of 3mg/kg and 30mg/kg, which also determine memory impairment, were effective. On the contrary, the DC-TA-46 dose determining memory impairment causes the highest increase in striatal cAMP level. Zaprinast is effective in increasing cGMP and cAMP concentration in both regions, but its efficacy in increasing cAMP cellular level is higher in the CP than in the HF. In both CP and HF zaprinast determines the highest increase in cAMP levels, at the same dose that impairs memory. Moreover, in the CP this drug determines an increase of both cyclic nucleotides. In the HF however, although the cGMP level is higher compared to controls, the difference is not statistically significant in all doses utilized. This is also supported by zaprinast inhibition assays of CP and HF cGMP and cAMP PDE activities, which demonstrate that this drug is less effective in inhibiting cGMP PDE activity in HF than in CP.

19. OREXIN - A ENHANCES DENTATE GRANULE CELL LONG TERM POTENTIATION. B.G. Smith; M.J. Wayner*; D.L. Armstrong; C.F. Phelix; Y. Oomura. Biology, Univ Texas San Antonio, San Antonio, TX, USA. Orexin-A is a hypothalamic peptide, localized in the lateral hypothalamic perifornical region. Axons containing orexin-A have been found throughout the brain and spinal cord. Two types of orexin receptors have been described in the rat brain, OX1R and OX2R. In the hypothalamus, OX1RmRNA is most highly concentrated in the ventromedial hypothalamic area. High levels of OX1RmRNA were also found in the tenia tecta, hippocampal formation, dorsal raphe, and locus coeruleus. Some of the perifornical neurons of the lateral hypothalamus project directly to the dentate gyrus and participate in the learning and memory process. It is quite possible therefore that a similar circuit exists for orexin-A containing perifornical neurons of the lateral hypothalamus and that they also project to the hippocampus where high levels of OX1RmRNA have been found. The purpose of this study was to determine the effects of orexin-A on hippocampal dentate granule cell long term potentiation (LTP) in vivo; in response to tetanization of medial perforant path afferents. Male Harlan Sprague-Dawley rats weighing between 300-375g were utilized. Animals were anesthetized using a dose of 1.4g/kg 25% urethane administered i.p. Standard surgical, stereotaxic, and electrophysiological procedures were utilized to induce LTP. Four doses of orexin-A; 30, 60, 80, 90, and 100nM were administered directly into the dentate gyrus. Enhancement of normal LTP occurred only at the 90nM dose and the facilitation was blocked by pretreatment with SB-334867, an OX1R antagonist. These results provide support for the hypothesis that the orexin-A neurons that project to the hippocampus participate in the learning and memory process.

20. LINKING THE P300 EVENT RELATED POTENTIAL IN RATS TO PRIMARY AND CONDITIONED REINFORCING STIMULI. Schneider, B.; Klipec W.D.; Franck, L. Dept. of Psychology, Drake University, Des Moines, IA, USA 50311. The human P300 Event Related Potential (P300 ERP), is thought to reflect an underlying cognitive process. Several experiments in our laboratory have demonstrated a robust P300 ERP in rats, the amplitude of which is directly related to the acquisition, extinction and reacquisition of control by a discriminative stimulus. Moreover, P300 amplitude is greater to the click of the food hopper (secondary reinforcer) than a tone that precedes lever insertion that sets the occasion for the response (tertiary reinforcer). The present experiment is a systematic replication of the previous work designed to eliminate multiple cues for food reinforcement, and measure a P300 ERP to the actual appearance of the food pellet. In the previous experiments, retraction of the lever and the click of the food hopper predicted food delivery. In the present experiment, using six rats, the lever retraction was delayed to eliminate this redundant cue. A non-target stimulus (white noise burst) was used as a truly random control. Lever insertion, used as a target stimulus, occurred on a variable time schedule at an 8:1 non-target to target ratio. A 4-KHz tone predicted the delivery of the food reinforcer which was delivered by a relatively silent dispenser. P300-ERPs were recorded to all stimuli. A large P300 ERP (about 100-microvolts) was measured about 300-msec after the food pellet appeared in the feeder tray. By manipulating delay of reinforcement, with an ABA reversal design, we found the P300 latency covaried perfectly with reinforcement delay. Reviewed collectively, these data support the hypothesis that the P300 represents a brain response to the recognition of reinforcing stimuli.

21. A NONHUMAN PRIMATE MODEL OF THE ANTEROGRADE AND RETROGRADE AMNESIA PRODUCED BY CONVULSIVE TREATMENT. *Moscrip, T.D.; *Terrace, H.S.; †Sackeim, H.A.; †Lisanby, S.H.; Department of Biological Psychiatry, New York State Psychiatric Institute; *Department of Psychology, Columbia University; †Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, New York, 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 smaller cortical and subcortical area and may result in less severe or persistent cognitive side effects than conventional ECT. The aim of this pilot study was to develop a nonhuman primate model sensitive to the amnesic effects of electroconvulsive shock (ECS) and magnetic seizure induction. Over several months, rhesus macaques were trained on three tasks of increasing complexity: a long-term memory task which required selection of a constant target from a background of distracters (akin to recognizing one's name), a short-term memory task which involved learning a new target each day against a variable number of distracters (akin to trial-and-error learning), and a combined anterograde and retrograde memory task where learning and memory were evaluated for new and previously trained 3-item lists. Monkeys were trained and tested twice daily, using either a short or long retention interval. Retention of recent and old 3-item lists was impaired by ECS, while MST resulted in impaired memory for new lists only. Additionally, ECS (but not MST) impaired subjects' ability to discriminate a variable target from distracters in the long-interval condition. These preliminary findings suggest that MST and ECS result in different profiles of acute cognitive impairment, and that the cognitive effects of convulsive therapy may be lessened by use of novel forms of seizure induction.

22. GLUCOSE TRANSPORTER PLASTIC CHANGES IN THE HIPPOCAMPUS FOLLOWING MEMORY PROCESSING. Messier, C.; Choeiri, C.; Staines, W.M. School of Psychology and Dept. of Molecular Medicine, University of Ottawa, CANADA. Glucose is the main metabolic substrate of the brain. Local cerebral glucose uptake (LCGU) vary according to metabolic requirement and is often taken as an index of neuronal activity.

Cerebral changes in LCGU may be due to changes in blood flow, glucose phosphorylation or glucose transport activity. In the present experiment we used semi-quantitative immunohistochemistry to measure the three glucose transporters most abundant in the brain (GLUT1, GLUT3 and GLUT4) immediately, 220 min or 24 hrs following training in an appetitive operant bar-pressing task. Sham-trained animals for each time point were included as well as a deprived untrained control group. Brain structures were identified with a stereotaxic atlas and pictures were taken using the image analysis program Northern Eclipse. The quantification was undertaken using the Image Tool Software. GLUT1 levels were increased, relative to the corresponding learning control, in the CA1 pyramidal and stratum radiatum cell layers as well as in the motor cortex. However, at longer delays following learning, GLUT1 levels decreased significantly in various brain regions. At 220 min delay, GLUT1 levels are significantly lower in trained animals relative to the sham-trained animals in the CA3 stratum radiatum cell layer. At 24 hrs following learning, GLUT1 levels decreased significantly in the frontal and motor cortices as well as in dorsal putamen. We did not see many significant changes in GLUT3 and GLUT4 levels but the variability of these measurements was noticeably higher. The results show that glucose transporter changes may underlie some of the changes in LCGU during brain activation.

23. RATS WITH DORSAL, BUT NOT COMPLETE, HIPPOCAMPAL LESIONS SHOW TEMPORALLY GRADED RETROGRADE AMNESIA ON A PLUS MAZE SPATIAL TASK. L.W. Means* & M.R. Hoane. Depart. of Psychology and Neuroscience Program, East Carolina University, Greenville, NC 27858 USA. Previously we demonstrated that rats with electrolytic lesions of the dorsal hippocampus (DH) can acquire a spatial task in an elevated “+”-shaped maze, whereas rats with lesions of the complete hippocampus (H) cannot. In the present experiment, rats were trained on the same task, and 1, 32, or 64 days following acquisition they received electrolytic lesions of the DH, H, or sham operations. For rats with lesions of the DH, the longer the training-surgery interval the better was the postoperative performance. Retention, reacquisition, and acquisition of the same task in another room all improved as the training-surgery interval increased. For rats with lesions of the H, post-operative performance was poor, regardless of the training-surgery interval. They showed no retention and were unable to reacquire the task or acquire the task in another room. Thus, only rats with lesions limited to the DH demonstrated temporally graded retrograde amnesia. These data suggest that temporally graded amnesia only occurs if the portions of hippocampus essential for original acquisition remain intact. This observation is consistent with the multiple trace explanation for amnesia following damage to the hippocampal memory system. Funded by an East Carolina University grant.

24. EFFECT OF BEHAVIORAL DESPAIR ON NAVIGATIONAL LEARNING IN FEMALE WISTAR RATS. Canbeyli, R.; Aksoy, A.; Kumru, G.; Yapıcı, N.; Açıık, A.; Baran, B.; Ozcelik, S. Psychobiology Laboratory, Department of Psychology, Bogazici University, Istanbul, Turkey. The study assessed the impact of behavioral despair (as measured by two forced swim tests) on navigational learning in the Morris Water Maze (MWM) with a hidden platform. In the first phase of the experiment, adult female Wistar rats (n=14) first underwent two forced swim tests separated by 24 hr and were tested a week later in the MWM for 12 days (5 trials per day) together with a control group (n=7) that was not previously subjected to forced swim tests. A day later, all subjects were tested for 2 min in the MWM with the platform removed. A week later, in the second phase, the control group from Phase I and a MWM-naïve group of animals (n=7) underwent two forced swim tests separated by 24 hr. In the first phase, when performance in the MWM was evaluated according to whether the experimental subjects displayed short (n=7) or long duration (n=7) of immobility in the second forced swim test, which is an indication of the degree of behavioral despair, the latter subjects showed a significant impairment in navigational learning compared to the former group and the controls. In the second phase, similar durations of immobility were displayed in the two swim tests by the MWM-naïve and MWM-experienced groups. These results indicate that in female Wistar rats the degree of behavioral despair has an impact on subsequent navigational learning in the MWM, but previous acquaintance with the MWM does not affect induction of behavioral despair. (Supported by Bogazici University ARFON/BAP Grant 00R103 to RC).

25. OPERANT ANALYSIS OF COGNITIVE BEHAVIOURS DEPENDENT UPON FRONTOSTRIATAL AND HIPPOCAMPAL SYSTEMS OF THE BRAIN. Sloan, H.L.; Dunnett, S.B. The Brain Repair Group, Cardiff University, Cardiff, CF10 3US, U.K. The prefrontal cortex and hippocampus have been implicated in various aspects of cognition including memory, attention, executive function and set-shifting. To investigate their involvement further this study examines the cognitive sequelae of lesions of these areas in the rat. The goal is to develop a robust operant test in which performance is differentially affected by either lesion. 32 rats were trained on an operant delayed matching to position task (DMTP) which allows working memory to be assessed over a range of delays. Rats were divided into 4 performance matched surgery groups and received bilateral sham or toxin (Ibotenic acid) lesions of the hippocampus or the prefrontal cortex. 2 weeks after surgery rats were tested on a hippocampal-sensitive reference memory version of the water maze to verify hippocampal lesion placement. This study is ongoing and rats will be subjected to a spatial reversal which is predicted to reveal a prefrontal deficit. Following water maze testing rats will be retested on DMTP after which the rule will be reversed to delayed non-matching to

position (DNMTP). Previous work suggests that control animals can readily adapt to this rule reversal; the switch from DMTP to DNMTP serves as an analogue to the Wisconsin Card Sorting Test in humans and is hypothesised to also be sensitive to prefrontal disruption in rats. The results will be discussed in terms of identifying tasks that yield anatomically dissociable deficits that can then provide the basis for establishing the efficacy of neuroprotective drugs and studying novel treatment strategies such as cell transplantation. This work is supported by Acadia Pharmaceuticals, San Diego, California.

26. D1, BUT NOT D2, D3, OR D4 RECEPTORS, ARE ESSENTIAL FOR DISRUPTION OF PREPULSE INHIBITION BY COCAINE IN MICE. ¹Lehmann-Masten, V.; ⁵Ralph-Williams, R.; ⁶Klamer, D.; ²Otero-Corchon, V.; ³Grandy, D.; ^{2,4}Low, M.J.; ¹Geyer, M.A. ¹Dept Psychiatry, University of California San Diego, La Jolla, CA, 92093 USA. ²Vollum Institute, ³Dept Physiology and Pharmacology, and ⁴Dept Behavioral Neuroscience, Oregon Health and Science University, Portland, OR 97201 USA. ⁵Dept Psychiatry, Harvard Medical School, Belmont, MA 02498 USA. ⁶Dept Pharmacology, Göteborg University, Göteborg, Sweden. Deficits in prepulse inhibition (PPI), an operational measure of sensorimotor gating, are characteristic of schizophrenia and related neuropsychiatric disorders. Clinical and animal studies have demonstrated a contribution of dopamine (DA) and the D2-family of DA receptor subtypes to the modulation of PPI, while little is known about the role of D1-like DA receptors. Using genetically altered mice, we have shown that the DA D2 receptor subtype (D2R) is necessary for amphetamine to exert its disruptive effects on PPI. In contrast, both the direct D1 DA agonist SKF82958 and the mixed D1/D2 DA agonist apomorphine disrupt PPI in wildtype (+/+) or D2R knockout (-/-) mice, but are ineffective in DA D1 receptor (D1R) -/- mice. To further examine the contributions of DA receptor subtypes in the modulation of PPI, D1R, D2R, D3 receptor (D3R), and D4 receptor (D4R) +/+ and -/- mice were tested with the indirect DA agonist cocaine in the PPI paradigm. Cocaine produced decreases in PPI in D3R and D4R mice regardless of genotype. Similarly, cocaine reduced PPI in both the D2R +/+ and -/- mice, even though amphetamine was ineffective in the same D2R -/- mice. Surprisingly, mice lacking the D1R failed to show a cocaine-induced disruption of PPI, demonstrating that the D1R may have a critical role in modulating the effects of cocaine on PPI in mice.

27. HALOPERIDOL ANTAGONISES AMPHETAMINE INDUCED DISRUPTION OF LATENT INHIBITION IN CONDITIONED TASTE AVERSION. Russig, H; Kovacevic, A.; Murphy, C. A.; Feldon, J. Laboratory of Behavioral Neurobiology, Swiss Federal Institute of Technology (ETH Zurich), Schorenstrasse 16, CH-8603 Schwerzenbach, Switzerland. Latent inhibition (LI) describes a process by which repeated pre-exposure of a stimulus without any consequence retards the learning of subsequent conditioned associations with that stimulus. It is well established that LI is impaired in rats and in humans by injections of the indirect dopamine agonist amphetamine (AMPH), and that this disruption can be prevented by co-administration of the typical neuroleptic haloperidol (HAL). Most of what is known of the pharmacology of LI is derived from studies using either the conditioned emotional response or the conditioned active avoidance paradigm. The goal of the present study was to determine whether these results would generalize to the conditioned taste aversion assay. We tested whether AMPH (0.5 mg/kg) pretreatment would disrupt LI of a conditioned aversion to sucrose, and if so, which stage of the procedure is critical for mediating the disruption; in addition, we tested whether HAL (0.2 mg/kg) could restore such an expected LI disruption. We determined that AMPH disrupted LI when it was injected before preexposure and prior to conditioning, but not if the rats were injected before either stage alone. When HAL was given 40 min before AMPH (before both preexposure and conditioning), it blocked LI disruption. These results are in line with the pharmacology of LI as derived from other conditioning paradigms. We conclude that the pharmacological regulation of LI in the CTA paradigm is similar to what has been observed previously in the conditioned emotional response and the conditioned active avoidance paradigms.

28. DIFFERENTIAL EFFECTS OF METHAMPHETAMINE AND COCAINE ON RATS' DISCRIMINATION PERFORMANCE IN Y-MAZE AND TWO LEVER CHOICE PARADIGMS. Dolezal, A; Klipec, W.D.; Mejia, R. Drake University, Dept. of Psychology, Des Moines, IA, USA, 50311. Previous research in our laboratory reported that d-amphetamine but not cocaine (COC) disrupted rats' discrimination performance in a Y-Maze. In a systematic replication and extension, six rats in each drug group were trained to run to the lighted arm of a Y-maze for water reinforcement using a 90% correct choice criterion. The rats were tested with an ascending then descending series of methamphetamine (METH) (0.56 to 3.0 mg/kg) and COC (3.0 to 30 mg/kg), with saline and no injection days interspersed. METH produced a dose dependent decrease in correct choices while COC produced no systematic breakdown in discrimination performance. COC produced a dose dependent decrease in latency, while METH produced a dose dependent increase in latency with focused stereotypies occurring at the 2.0 and 3.0 mg/kg doses. In Experiment 2, the same rats were trained in operant chambers to choose between lighted and unlighted levers. The levers were inserted together after an inter-trial interval. If the rat chose the lighted lever, the unlighted lever retracted and water was delivered on a VI 10-sec. schedule for responding on the lighted lever. If the rat chose the unlighted lever, both levers retracted for a fifteen-second blackout. After attaining a stability criterion, rats were tested with an ascending then descending dose series similar to Experiment 1 with a high METH dose of 2 mg/kg. While neither drug produced a systematic breakdown in discrimination performance, both METH and COC

significantly decreased responding during the VI schedule. Both drugs showed sensitization to low doses on the descending series in each experiment.

29. BLOCKADE OF THE MOTOR STIMULANT EFFECTS OF AMPHETAMINE BY GROUP I, GROUP II, AND GROUP III METABOTROPIC GLUTAMATE RECEPTOR LIGANDS IN THE RAT NUCLEUS ACCUMBENS : POSSIBLE INTERACTIONS WITH DOPAMINE RECEPTORS. David, H.N.; Abraini, J.H. UMR CNRS 6551, CYCERON, Université de Caen, Caen, France. Previous investigations have shown that mGlu receptors would be involved in the amphetamine-induced motor response. However, data are somewhat controversial across studies where methodological protocols vary. The aim of the present study was to determine the involvement of mGlu receptors in the NAcc in the locomotor-activating properties of amphetamine in rats exposed to similar experimental conditions and well habituated to their experimental environment, a condition known to modulate the motor response to amphetamine. Focal infusion of the group I mGlu receptor antagonist S-4-CPG, which has no effect on basal motor activity, virtually suppressed the locomotor response to amphetamine, while infusion of the group II mGlu receptor antagonist LY 341495 or the group III mGlu receptor agonist AP4, at the minimal dose that produces locomotor activation, reduced it by approximately a half. These effects were blocked by the group I mGlu receptor agonist DHPG, the group II mGlu receptor agonist APDC, and the group III mGlu receptor antagonist MPPG, respectively. These data confirm that mGlu receptors in the NAcc contribute to the psychostimulant motor effect of amphetamine. Results are discussed at the view of recent neuropharmacological studies that have defined the effects of these mGlu receptor ligands on basal motor activity and DA receptor agonists-induced locomotor responses in rats exposed to similar experimental procedures (David and Abraini, 2001a,b, 2002). It is suggested that the contribution of mGlu receptors to the amphetamine-induced motor response may result mainly from their functional, either direct or indirect, interactions with D1-like receptors in the NAcc.

30. HIPPOCAMPAL SEROTONIN AND THE ACUTE BEHAVIORAL EFFECTS OF COCAINE: EVIDENCE FROM IN-VIVO MICRODIALYSIS STUDIES. Müller, C.P.¹; Carey, R.J.²; Huston, J.P.¹ ¹ Institute of Physiological Psychology I and Center for Biological and Medical Research, University of Düsseldorf, Germany; ² VA Medical Center and SUNY Upstate Medical University, Syracuse, USA. The hippocampus is an important structure for learning/memory and locomotor activation, which receives a dense serotonergic (5-HT) innervation. 5-HT_{1A} receptors are found in high density as postsynaptic receptors in terminal regions of the 5-HT projections, such as the hippocampus, and as somatodendritic autoreceptors in the raphe nuclei. Using in-vivo microdialysis in freely moving rats, we showed that systemic administration of the 5-HT_{1A}-receptor agonist 8-OH-DPAT (0.2 mg/kg, i.p.) potentiates cocaine (10 mg/kg, i.p.)-induced hyperlocomotion while attenuating the cocaine-induced 5-HT increase in the hippocampus. Local application of 8-OH-DPAT (0.1-10 μM) into the hippocampus by reversed dialysis also attenuated the cocaine-induced 5-HT increase in the hippocampus. However, it inhibited the cocaine-induced hyperlocomotion. These results support a role of the hippocampus in the acute cocaine effects on behavior and on 5-HT release. They suggest an inhibitory role for hippocampal 5-HT_{1A}-receptors in cocaine-induced hyperlocomotion and the hippocampal 5-HT response. At the same time results provide evidence for a dissociation in the contribution of different 5-HT_{1A}-receptor populations to the acute behavioral effects of cocaine.

31. THE TIME COURSE OF EFFECTS FOLLOWING THE ADMINISTRATION OF METHYLENEDIOXY-METHAMPHETAMINE, 'ECSTASY', ON CENTRAL NERVOUS SYSTEM MONOAMINE CONTENT, PITUITARY ACTIVATION, AND ADRENAL OUTPUT ON POSTNATAL DAY 11 IN RATS. Williams, M. T. ; Schaefer, T. L.; Ehrman, L. A.; Sah, R.; Gudelsky, G. A.; Vorhees, C. V. Cincinnati Children's Research Foundation and Univ of Cincinnati College of Medicine, Cincinnati, OH. Methylendioxyamphetamine (MDMA) administration to rats from postnatal day (P) 11-20 produces deficits in spatial and sequential learning and memory. Concurrent with the deficits in learning and memory are minimal decreases in monoamine content within the hippocampus, however these decreases are not correlated with the learning and memory deficits. Recent data suggest that early changes to monoamines, especially serotonin, can produce lasting effects on learning and memory. Furthermore, high levels of adrenal hormones in neonates are known to alter hippocampal development. In this study we administered MDMA (10 mg/kg, expressed as the freebase) or saline to entire litters (n=8/treatment) every 2 hours for 6 hours. Trunk blood, striatum, hippocampus, and thymus were collected from a male and female pair within each litter at 1, 7, 24, 30, or 78 hours after the first dose. Increased ACTH was observed at the 1 and 7 hour time points with corticosterone increased as well but elevated for a longer period (24 hours). Reductions in serotonin and its metabolite, 5-HIAA, were observed in the hippocampus starting at 1 hr and in the striatum reductions were observed for DOPAC at 1 hr, 5-HIAA at 7 hours, and 5-HT at 24 hours. No treatment-related changes in dopamine were observed. Serotonin transporter changes will be discussed. These data suggest that there are early adrenal and monoamine changes that may underlie the learning and memory deficits produced by MDMA.

32. U-69593, A KAPPA-OPIOID AGONIST, DECREASES COCAINE-INDUCED LOCOMOTOR ACTIVITY IN ESTROGEN PRIMED FEMALE RATS. Puig-Ramos, A.; Bruckman, W.J.; Santiago, G.S.; Segarra, A.C. Dept. of Physiology, MSC, Univ. of PR, San Juan, PR and Dept. of Biology, Univ. of PR, San Juan, PR. Studies in male rats

indicate that mu and δ -opioid receptors exert opposing effects on cocaine-induced locomotor activity. Previous results in our laboratory indicate that nalozonazine, a mu-opioid antagonist, decreases cocaine-induced locomotor activity and sensitization in the female, an effect dependent on plasma estrogen levels. This study was designed to investigate if the kappa opioid system participates in modulating cocaine-induced locomotor behavior in the female. Adult Sprague-Dawley rats were ovariectomized (OVX), half received Silastic implants with estradiol benzoate(OVX-EB), the other half received empty implants(OVX). After recovery and habituation to the activity chambers, rats were injected daily with vehicle or U-69593(0.32 mg/kg, i.p.)15 min prior to cocaine (15 mg/kg,i.p.). Locomotor activity was measured for 60 min on day 1, 3, 5 and, after 2 days of cocaine withdrawal, on day 8. At all days tested, U-69593 diminished cocaine-induced locomotor activity in rats that received estrogen, similar to results obtained in males, but had no effect in females devoid of estrogen. These results indicate that estrogen affects δ -opioid modulation of cocaine-induced locomotor activity and stress the importance of conducting studies in females before considering the use of mu and δ -opioid receptor ligands as therapeutic agents for the treatment of addictive disorders.

33. GENES ENCODING PROTEINS WITHIN THE NUCLEUS ACCUMBENS SUBREGIONS ARE AFFECTED BY REINSTATEMENT OF COCAINE-SEEKING BEHAVIOR. Ramos, D.L.; Félix, J.; Al-Banchaouchi, M.; Menéndez, R.; Moulder, J.K.; Otero, J.M.; Jiménez, D.M.; Peña de Ortiz, S.; Maldonado-Vlaar, C.S. Department of Biology, University of Puerto Rico. Molecular studies have implicated several immediate early genes and neuropeptides in eliciting cocaine reward. These experiments are aimed at further characterizing which genes within the nucleus accumbens subregions (NA) may be involved in eliciting cocaine-seeking behavior induced by environmental stimuli. In Exp. I naïve rats were sacrificed and their brains sectioned and stained with thionin. Slices were examined under a microscope and laser capture microdissection (LCM) was utilized to collect cells from specific NA core and shell areas. RNA extraction was conducted followed by Real Time PCR. Primers for neurotensin and other housekeeping genes were designed and used. Preliminary results showed good RNA extraction from these cells following LCM, and the presence of rat-GAPDH gene in both core and shell. In Exp. II rats were implanted with intravenous jugular catheters. Following recovery from surgery, rats were trained to discriminate two different environments with either saline or cocaine intravenous infusions until stable baseline. The rats went through extinction phase. When extinction criterion (5 presses/5 days) was reached, rats were reinstated only with the presentation of cocaine-paired cue. All animals showed reinstatement behavior. Brains of reinstated rats were processed as in Exp. I Ongoing studies will examine which genes are being regulated by cocaine-seeking behavior. We hypothesize that neurotensin gene will show an up-regulation following the exposure to environmental stimuli previously associated to cocaine reward.

34. DOPAMINE D3 RECEPTOR INVOLVEMENT ON SELECTIVE ATTENTION, IN THE RAT. Casarrubea, M.; Saia, V.; Sorbera, F.; Crescimanno, G. Department of Experimental Medicine, Human Physiology Section, University of Palermo, Italy. Strong evidence has been found out for the existence of dopamine involvement in attentive function. In particular, the mesolimbic-mesocortical dopaminergic (DA) system seems to play a key role on selective attention. Moreover, in mesolimbic DA circuits a close association with D3 receptor subtype has been observed. However, no data exist on possible involvement of this D2 receptor family subtype on attention focusing. To shed light on the matter, effects of acute administration of PD 128907, a D3 agonist, were studied on specific parameters of an acoustically evoked attentive behavior, on rats. Four groups of Wistar rats were administered IP different doses of the drug (0.25, 0.5, 1 and 2 mg/kg); one more group was acoustically stimulated and received vehicle. Following drug injection, acoustic stimuli (300 Hz, 2 sec) were randomly delivered both for spatial localization and intertrial interval. By means of a videorecording and videoanalysis apparatus, two parameters were analysed during sessions lasting 20 min: focusing latency (FL) (interval between the end of head orienting movement following acoustic stimulation and beginning of attention focusing) and focusing duration (FD) (interval between beginning and end of attention focusing behavior). Attention focusing behavior consisted of auricles erection, head oriented toward stimulus source, body immobility, sniffing. In control group, mean + S.E. of FL was 1.601 + 1.1 s, and mean + S.E. of FD was 10.138 + 1.11 s. Following PD 128907 mean FL showed a dose-dependent increase except when the lowest dose was used. As for FD, the two lowest doses provoked a decrease, whereas only the highest one induced an increase. Drug effect could be explained with a role of mesolimbic D3 receptor in the central mechanisms involved in focused attention. As for the different and dose-dependent effects, they could depend on pre- or post-synaptic activity of the drug.

35. EFFECTS OF MICROGRAVITY ON ORIENTING REACTION, IN THE RAT. Adamo, L.; Casarrubea, M.; Conti, M.; Fazio, G.; Adamo A.; Mazzola, C.; Crescimanno, G. Dept. of Experimental Medicine, Human Physiology Section, University of Palermo, Italy. Head turning (HT) movement is a component of the orienting reaction towards acoustic stimuli. Rat's orienting behavior has been investigated under gravity conditions, however, scanty data exist on possible changes of the response under microgravity. Aim of the research was to analyse HT latency and duration following acoustic stimulation and under microgravity. Experiments were carried out during the 4th ESA Student Parabolic Flight Campaign on 4 male Wistar rats. About 3.5 s after the beginning of zero-g, we

delivered rats an acoustic stimulus (300 Hz, 2 s) via loud speakers connected to an acoustic stimulator. Responses were recorded on videotape by means of an infrared, fixed video camera linked to a soundproof, thermostatic experimental cage. To avoid animal habituation, stimulations were randomized as for spatial localization and alternation of parabolas with stimuli or without. A comparison was made between data obtained under microgravity and the ones obtained on a different group of 6 rats under gravity. Under gravity condition, mean HT latency + S.E. was 178.03 + 17.95 ms, and mean HT duration + S.E. was 332.54 + 18.12 ms. Under microgravity, a significant increase of both parameters was observed: mean HT latency + S.E. was 535.42 + 53.30 ms, ($p < 0.0001$) and mean HT duration + S.E. was 462 + 29.65 ms, ($p < 0.001$). Significant modifications in the activity of vestibular system and muscular proprioceptors, localised in animal's head and neck, and therefore in cerebellar activity, could explain the results. Research supported by University of Palermo, Italian Space Agency and European Space Agency

36. VISUAL-MOTOR INTEGRATION: A MODIFIED LINE BISECTION TEST IN A NORMAL POPULATION. Bloomer, R.; Pezzulo, P. Visual-motor coordination has been found to involve a neural circuit including the frontal eye fields and the fastigial nucleus of the cerebellum. The line bisection task is a measure of visual-motor integration and has often been in used cases of brain damage to observe hemi-inattention, particularly in cases of parietal lesion. Unfortunately the error variance in early forms of line bisection tests has been found to exceed 50%. We developed a highly reliable (.93) Modified Line Bisection Test (MLBT), by increasing the size, number, and variability of lines, by using both preferred and non-preferred hands, and by scaling deviations in jnd's following the Weber-Fechtner law. We administered the MLBT to a sample of 340 children and youth ranging from grade 1 to college freshman. The Mblt, in addition to maintaining it's potential for detecting hemi-inattention, also provides reliable data on visual-motor development. We present developmental data on visual-motor deviation in jnd's related to handedness, and to academic achievement, and confirm the right deviation tendency reported in the literature.

37. PREFRONTAL REGULATION OF POSTERIOR PARIETAL ACETYLCHOLINE RELEASE. Nelson CL; Sarter M; Bruno JP. Depts. Of Psychology and Neuroscience, The Ohio State University, Columbus, OH, 43210. Attentional functions involve the detection and selection of stimuli and the allocation of processing resources for competing tasks. Attention is subject to "top-down" regulation by the prefrontal cortex (PFC), optimizing knowledge-driven processing in posterior sensory and associational areas, including the posterior parietal cortex (PPC). As cortical acetylcholine (ACh) release, originating from the basal forebrain cholinergic system (BFCS) has been demonstrated to mediate attentional processing, we investigated the effects of local stimulation of the PFC on ACh release in the PPC. Stimulation of the PFC with perfusion of AMPA through the dialysis probe increased ACh efflux in the PPC, whereas perfusion of NMDA resulted in no change, possibly attributable to a lack of sufficient endogenous activation of the cortical projection neurons. Perfusion of the muscarinic agonist carbachol in the PFC increased ACh efflux in the PPC, whereas perfusion of nicotine had no significant effect. We are currently investigating the potential factors underlying the differential contributions of cholinergic receptor subtypes in the PFC, including the contributions of other neurotransmitters in the PFC (i.e. dopamine). These studies will begin to elucidate the top-down regulation of attentional functions, particularly in terms of cortico-cortical interactions and the BFCS, and will contribute to an understanding of the consequences of PFC dysfunction on attentional processing. (Supported by MH57436, MH063114, NIA10173, NS37026)

38. MODULATION OF CORTICAL ACETYLCHOLINE RELEASE BY NUCLEUS ACCUMBENS NMDA RECEPTORS. Gatien ML; Sarter M; Bruno JP. Depts. Of Psychology and Neuroscience, The Ohio State University, Columbus, OH, 43210. Attentional functions rely on the integrity and activation of the basal forebrain cholinergic system (BFCS), including its projections to the prefrontal cortex (PFC). The nucleus accumbens (NAC) receives input from the prefrontal cortex and other telencephalic regions and, via its GABAergic efferent projection to basal forebrain, is an important modulator of the excitability of the BFCS. Intra-accumbens administration of the NMDA receptor antagonist D-CPP has been shown to dose-dependently increase cortical acetylcholine (ACh) efflux in PFC by as much as 200% (200iM). The current experiment utilized dual cannula microdialysis to examine the effect of intra-accumbens perfusion of NMDA on ACh efflux in PFC. Surprisingly, our recent findings indicate that intra-accumbens perfusion of NMDA also increases basal cortical ACh efflux in a dose-dependent fashion, with increases exceeding 200% at the highest dose (250iM). Because glutamate mediated effects can be modulated by dopamine D1 and D2 receptor activity in NAC, ongoing dual cannula microdialysis experiments are determining the ability of intra-accumbens dopamine receptor manipulations to modulate the NMDA-induced increase in cortical ACh efflux. Collectively, these findings may contribute to an understanding of NAC control of the excitability of the BFCS and their role in dysfunctions of attentional processes. (Supported by MH057436)

39. ORGANIZING A SATELLITE IBNS CLUB AT YOUR UNIVERSITY. Risbrough, V.; Evans, J.; Henry, S.; Ong, J.; Geyer, M. Departments of Neurosciences and Psychology, University of California, San Diego, La Jolla, CA, 92093. Behavioral neuroscience is a field that crosses many disciplines, including biology, cognitive science, neuroscience and psychology. Behavioral neuroscience is also a field requiring extensive training in technique,

experimental design, and statistical analysis. Therefore, increased awareness of the local behavioral research community may (1) increase incoming graduate students' interest in behavioral neuroscience (2) improve training and breadth of techniques for new scientists and (3) foster increased collaboration and communication between the local behavioral neuroscience community. To this end, organizations such as local behavioral neuroscience clubs can be of great benefit to the behavioral neuroscience field as well as the local neuroscience community. We have set out to organize a student-run satellite club of the International Behavioral Neuroscience Society (IBNS) at the University of California San Diego. The goals of the club are: (1) to create a website which will include a listing of behavioral neuroscientists on campus and their specialization, upcoming events and speakers, as well as upcoming national and international meetings, job postings and funding resources; (2) to foster increased awareness of the behavioral neuroscience community on campus through quarterly speaker presentations; (3) to encourage debate and dissemination of information on ethical issues in scientific research (e.g., experimentation on animals, stem cell research, etc.). We have developed a protocol for registering the club, web site design, and potential funding resources. By presenting this information we hope to encourage IBNS members to organize similar clubs in their own academic communities.

40. THE HUMAN HPLC COLUMN: "MINDS-ON" NEUROSCIENCE FOR THE NEXT GENERATION. Frantz, K.; Rose, J. Georgia State University and the Center for Behavioral Neuroscience, Atlanta, GA 30303-3088 USA. The intent of this educational endeavor was to promote student learning about the acute- and long-term effects of drugs of abuse and how those effects are examined in the laboratory. The innovation was to use a "hands-on, minds-on" activity within the lesson. A neuroscientist visiting middle and high school classrooms began with a brief lecture on neuroanatomy, reward circuitry, and measuring neurochemistry in vivo with microdialysis. Then students became a "human HPLC column"; they learned how to act out components of the column and its stationary phase, regulate passage of "molecules" (other students) down the column, collect data on retention time for different types of molecules (i.e. dopamine and its metabolites), and graph the results. Beyond imparting valuable information on detrimental drug effects, such dynamic lessons in neuroscience led by active researchers improve attitudes toward science, increase science literacy, and elevate awareness of career opportunities in science. Teaching neuroscience in an interactive format may also sharpen students' social and leadership skills, and this is known to contribute to drug abuse prevention. By partnering with a specialized neuroscientist, school teachers gain content knowledge and see demonstrations of in-class activities that not only satisfy their state and national curriculum standards but also ignite their students' interest in science. Neuroscientists are able to attract young students to their fields, begin training the next generation of specialists, and gain significant teaching experience. Creating the human HPLC column is mutually beneficial to all parties involved in the educational process.

Friday, April 25:

8:00-10:00 Symposium 2: *Nonlinear and advanced behavioral assessment methods and their implications for behavioral neuroscience.*

COMPLEXITY AND BEHAVIORAL ORGANIZATION IN RODENTS. Paulus M.P.; Powell S.B.; Geyer M.A. Human and animal behavior consists of complex sequences of observable events that are aimed to achieve a goal. One approach to quantify the sequences of behavior in rodents is to record sequences of motor behavior in space and time using photo-beam or video tracking systems, which yields a trajectory of the animal, i.e. a sequence of (x,y) positions in space over time. We have developed two approaches to quantify the spatio-temporal characteristics of the animal's trajectories. First, the spatial d approach is based on fractal dimension analysis and quantifies the degree to which the trajectory progresses along a straight line or is highly localized within a circumscribed area. Second, the dynamical entropy approach quantifies the degree to which nonlinear dynamical are unpredictable and measuring the number of different trajectories that the animal generates during the course of a session. Based on these measures, we are able to show that (1) dopaminergic agonists produce inverted U-shaped dose response curves for both spatial d and entropy in both rats and mice; (2) the complexity or behavioral organization of locomotor behavior in mice or rats is independent of the amount of locomotor activity; and (3) pharmacological agents that increase locomotor activity can be differentiated based on changes of either spatial d or entropy. These results support the conclusion that quantifying the spatio-temporal characteristics of an animal's locomotor trajectories can be used to (1) elucidate the effects of drugs on animal behavior; (2) develop new animal paradigms aimed to model specific aspects of neuropsychiatric disorders; and (3) determine which neural substrates are critical for the sequencing of behavior.

MEASURING LOCOMOTOR PATTERNS IN DOPAMINE TRANSPORTER KNOCKOUT MICE. ¹Powell, S.B.; ¹Paulus M.P.; ²Ralph-Williams, R.; ¹Lehman-Masten, V.; ³Caron, M.G.; ¹Geyer, M.A.; ¹Dept. of Psychiatry, UCSD, La Jolla, CA 92093 USA; ²Dept. of Psychiatry, Harvard Medical School, Belmont, MA 02478 USA; ³Dept. of Cell Biology, Duke University, Durham, NC 27710 USA. A key component of perseverative behavior, i.e. the aimless repetition of similar behavioral acts, is the abnormal sequencing of behavioral events. Dysfunctions of the dopamine

system in humans, e.g. schizophrenia and drug dependence, have been linked closely with perseverative behavior. One approach to the study of these types of behaviors has been to measure the structure of locomotor activity in rodents to dissect the effects of both pharmacological and genetic manipulations on the organization of behavior. Previous studies from our group have shown that dopaminergic and serotonergic compounds affect not only the amount but also the sequencing of locomotor behavior in rats and mice. In mice, both amphetamine and MDMA induce a behavioral profile of increased locomotor activity characterized by tight circling around the perimeter of the chamber in a repetitive, highly predictable fashion. Similarly, mice lacking the dopamine transporter (DAT) show profound increases in locomotor activity and repetitive circling. While previous studies have shown that the amount of locomotor activity can be reduced in DAT (-/-) mice with psychostimulants and serotonin uptake inhibitors, few studies have examined alterations in locomotor patterns in DAT (-/-) mice. Recently we have shown that perseverative patterns of locomotor behavior in DAT (-/-) mice can be reversed with dopamine D1 but not D2 receptor antagonists. Therefore, perseverative behavior observed in DAT(-/-) mice can be modified by targeted dopaminergic blockade. Studies are being conducted to clarify the role of serotonin on perseverative behaviors induced by a dysfunctional dopamine system.

MOTOR BEHAVIOR IN WILD AND LABORATORY RODENTS: STRUCTURE OF ENVIRONMENT AFFECTS THE SPATIAL DISTRIBUTION BUT NOT THE LEVEL OF ACTIVITY OR THE TEMPORAL ORGANIZATION OF LOCOMOTION. Eilam, D.; Szechtman, H.* Dept. of Zoology. Tel-Aviv University, Ramat-Aviv 69 978, Israel. *Dept. of Psychiatry and Behavioral Neurosciences McMaster University Hamilton, Ontario, Canada. Locomoting periods are analyzed to assess three independent properties of locomotion: (1) the level of activity; (2) the temporal (sequential) organization of locomotor bouts; and (3) the spatial distribution of locomotor paths. Activity, and temporal structure, are both relatively stable in normal (intact) behavior, showing relatively minor adjustments in conditions of substantial change in arena size. The adjustments are in inter-stop distance (distance traveled between successive stops) and in trip-length (distance traveled between successive stops at home base). In contrast, spatial distribution of motor behavior is more sensitive to environmental changes. When tested in daylight, normal (intact) rodents cling to the walls, especially in large arenas. However, when tested in the dark and/or when objects are added to the arena, activity increases dramatically, with the trajectories of locomotion converging to the objects (landmarks) as an expression of navigating while using landmarks and path integration. When sensitized to quinpirole (D2/D3 dopamine-receptor stimulant), rats develop path stereotypy that is attached to specific landmarks. Relocation of these landmarks induces adjustments in inter-stop distance and trip-length, forming new path stereotypy while preserving the same level of activity. Altogether, results in normal and in drug-induced motor behavior illustrate a behavioral stability in terms of activity and temporal structure, alongside adjustments of the spatial distribution of locomotion to the structure of the environment. Understanding the spatial distribution of motor behavior in terms of the shape and the distribution of paths of locomotion are therefore the key for uncovering the underlying mechanisms in motor behavior.

NON-LINEAR EFFECTS ON THE RETENTION OF AN AVOIDANCE RESPONSE INDUCED BY SHOCK LEVELS AND ANABOLIC STEROIDS. Isaacson, R. L. and Lewis, H. W. III In 2000 Isaacson presented a reanalysis of data gathered earlier in two experiments reported by Isaacson, Varner, Baars, and deWied (1995). The case was made in the more recent paper that traditional statistical analysis of the data based on traditional measures of central tendencies and standard deviations were not accurate representations of the behavior of the animals. Furthermore, the use of such common statistical techniques often, in fact, leads to misleading conclusions. In most experimental groups the behavior of the subjects was more compatible with non-linear approaches including the bifurcations as described in "Feigenbaum maps" or by the "movement" of animals from one "attractor" to another. The steroid-induced behavioral changes when interpreted as movement between attractors or the induction of bifurcations can be thought of as accelerating these processes. A more extensive examination of the data from the original experiment will be reported. This extension of the non-linear analysis will show the possibility that the data in some groups are reflecting the occurrence of multiple bifurcations occurring in some groups and the possible exhibition of "chaotic behavior" in certain other groups at drug doses at or near the transition point leading to a bifurcation in behavior. In the Feigenbaum model quasi-chaotic behavior is the immediate precursor of new bifurcations. The usefulness of non-linear analyses in examining behaviors will be demonstrated. In many instances the descriptions of behavior in non-linear terms may lead to new insights into the underlying behavior-related mechanisms. Some ways in which behavioral phenomena can be interpreted in non-linear terms will be described including the application of "fuzzy logic" principles.

A DYNAMICAL DISEASE MODEL OF STEREOTYPED BEHAVIOR: MEASURING COMPLEXITY AND REGULARITY. Lewis, M.H., Dept. of Psychiatry. University of Florida, Gainesville, FL, 32610; Bodfish, J.W., Dept. of Psychiatry, University of North Carolina, Chapel Hill, NC; Newell, K.M., Dept. of Kinesiology, Penn State University, University Park, PA, USA. In a dynamical disease model, illness can be characterized by strikingly periodic or predictable dynamics in relevant physiological systems. Healthy systems, however, are complex, variable and difficult to predict. We have applied a dynamical disease model to motor behavior in individuals with

developmental disorders who exhibit abnormal stereotyped behavior. Combining repeated measurements of behavior over time with non-linear dynamical analyses (approximate entropy or ApEn) has yielded several findings. First, kinematic and force platform analysis of body rocking both showed that this behavior, although highly periodic, is less regular than body rocking exhibited by healthy volunteers (higher ApEn). Second, compared to matched controls, individuals who engaged in stereotyped body rocking displayed postural control deficits when standing or sitting on the force platform. These differences included significantly increased amplitude and velocity of postural sway as well as markedly reduced complexity (lower ApEn) in the distribution of forces around a center of pressure. Viewed as a time series, these moment-to-moment forces were highly periodic compared to control series. These findings suggest that the dynamical disease model might be extended to behavioral disorders that, as a consequence of CNS insult, represent loss of variability or complexity in behavior replaced by highly repetitive, periodic actions. Evidence of a shift from complexity to regularity can be observed not only in the target behavior (i.e., stereotypy) but in other motor behaviors as well.

10:30-12:00 Oral Session 2: Ingestion.

EFFECTS OF GALANIN ON FEEDING BEHAVIOR IN THE MOUSE. Wrenn, C. C.; Holmes, A.; Saavedra, M. C.; Luo, M.; Sullivan, T.; Crawley, J. N. Section on Behavioral Genomics, National Institute of Mental Health, Bethesda, MD. The neuropeptide galanin stimulates feeding in satiated rats after central microinjection. To address the role of galanin on feeding in the mouse, we employed both genetic and pharmacological approaches. A transgenic line of mice that conditionally overexpresses galanin in noradrenergic and adrenergic neurons (GAL-tg) showed body weights similar to that of WT littermate controls from the ages of 9 to 42 weeks. The circadian pattern of ingestion of a liquid diet (Ensure) was assessed in GAL-tg mice over 24 hr in the Dilog lickometer apparatus. GAL-tg and WT mice did not differ in the number of meals, meal size, length of interval between meals, or total amount consumed over a 24 hr period. To examine the role of exogenous galanin on feeding behavior in mice, we injected doses of galanin or vehicle, into the lateral ventricles of satiated C57BL/6J mice. Preliminary results indicated that mice that received 0.5 nmole of galanin ate significantly more of a highly palatable cookie mash than vehicle injected controls. The present data suggest that exogenously administered galanin stimulates feeding in mice, but endogenous overexpression of galanin has no effect on feeding, possibly because of compensatory changes in other transmitter systems. (Supported by IRP, NIMH)

INCENTIVE MOTIVATIONAL PROPERTIES OF ALIMENTARY AND SEXUAL STIMULI: FUNDAMENTAL DIFFERENCES. Anders Ågmo, Department of Psychology, University of Tromsø, Tromsø, Norway. In the present series of experiments we exposed male rats to an entirely new alimentary stimulus, chocolate flavoured pellets, in one area of a large open field and to their standard food in another area. Sometimes the pellets were presented behind a wire mesh preventing consumption, and sometimes they were freely available. In other experiments, the alimentary stimuli were replaced by a receptive female and an intact male, respectively. The rats did not approach the chocolate pellets more than the standard food when they were unavailable for consumption. Previous home cage consumption of chocolate pellets as well as 12 hrs of food deprivation did not affect this. When the pellets were available for consumption there was no difference between chocolate and standard food in animals who never had tasted chocolate. After home cage consumption, there was a clear preference for chocolate pellets. Thus, the odor and/or flavour of chocolate do not have unconditioned incentive properties, but can acquire such properties through experience (learning). Furthermore, an alimentary stimulus has incentive properties only when available for consumption. When food was replaced by sociosexual incentives, we confirmed that an unavailable female was more approached than a male in rats without sexual experience. It is concluded that sexual stimuli, in contrast to alimentary, have incentive motivational properties that are not only unconditioned but also effective when they are unavailable for consumption. Finally, rats were allowed to freely consume chocolate pellets for 2 hours before test while others were allowed to copulate ad libitum for 4 hours. Pretest consumption of chocolate eliminated preference for it while extended pretest copulation failed to reduce the female's incentive value. Taken together these data show that alimentary incentive motivation is fundamentally different from sexual incentive motivation both with regard to the importance of consummation, the role of learning and to the effects of immediate preexposure.

EFFECT OF NEUROPEPTIDE Y MICROINJECTED INTO THE PVN ON THE CONSUMPTION OF ETHANOL OR FOOD. Lucas, L.A.C.; McMillen, B.A. The 36-amino acid peptide, neuropeptide Y (NPY), is a powerful orexic agent when microinjected into the anterior hypothalamus. Recent research suggested that differences in brain NPY content in genetic lines of drinking and non-drinking animals may account for differences in the consumption of ethanol. The following experiments tested whether or not the NPY-induced drive from the hypothalamus for food would influence the consumption of ethanol. A guide cannula was implanted in each male Wistar and mHEP rat aimed at the paraventricular nucleus (PVN) of the hypothalamus for microinjection of NPY, D-NPY₂₇₋₃₆ a d-threonine substituted fragment, or vehicle (pyrogen-free artificial CSF). Injection sites were confirmed by histology. In the Wistar rat, there was not a significant effect of 3.0 µg in 1.0 µl of NPY on the

consumption of ethanol. In the mHEP rat, 3.0 μ g D-NPY₂₇₋₃₆ caused a significant 54% decrease in ethanol consumption from baseline, but the response was not different from microinjection of vehicle. In food satiated Wistar rats, NPY induced feeding for a total of 20 g of food within 2 hr., which was blocked by D-NPY₂₇₋₃₆. Microinjection of D-NPY₂₇₋₃₆ decreased feeding in food deprived rats by 78% relative to microinjection of vehicle. Thus, the Wistar rat does not perceive ethanol as a source of calories or food and the consumption of ethanol cannot be driven by injection of NPY into the PVN. The effect of D-NPY₂₇₋₃₆ on ethanol consumption by the mHEP rat is not as robust as the effect of this drug on food consumption and this rat also may not perceive ethanol as a source of calories or food. (Authors thank J. W. Nyce & S. Leonard, Epigenesis, Inc., Princeton, NJ for synthesis of NPY and D-NPY₂₇₋₃₆)

INFUSING 5-HT_{2A} RECEPTOR ANTAGONISTS INTO THE BASOLATERAL AMYGDALA ENHANCES FEEDING. Coscina, D; Parker, G; Joshi, D. Dept. of Psychology, Wayne State University, Detroit, MI 48202 USA. We have previously reported that infusing metergoline, a 5HT_{1,2,7} antagonist, into the posterior basolateral amygdala (pBLA) elicits feeding for 1 hr in doses as low as 0.3 nM. Subsequent experiments have revealed that neither selective 5HT_{1B} nor 5HT_{1C} antagonists mimic this effect. The present work demonstrates that local infusions of the 5HT_{2A} antagonists, ketanserin (KET; 30 nM but not 3 nM) or 4-(4-fluorobenzoyl)-1-(4-phenylbutyl)-piperidine oxalate (44F; both 30 and 3 nM), elicit feeding for 1 hr following pBLA injections. Videotapes of these feeding tests were also analyzed to determine the frequency of the following behaviors (Fray scoring): inactivity, locomotion, rearing, sniffing, grooming, gnawing polystyrene chips, gnawing/eating food, and drinking water. The feeding ineffective dose of KET (3 nM) suppressed inactivity and enhanced both rearing and sniffing. The feeding effective dose (30 nM) enhanced inactivity while suppressing rearing and sniffing. The low feeding effective dose of 44F (3 nM) produced no behavioral changes compared to vehicle infusions. The higher dose (30 nM), which elicited the same amount of feeding as the 3 nM dose, enhanced inactivity while suppressing rearing and sniffing. Since 44F is a more selective 5HT_{2A} antagonist than KET, these data show that impeding neurotransmission at pBLA receptors can enhance food intake without inducing behavioral indices of non-specific arousal or heightened motor activity. This implies a relatively selective mechanism of action by 5HT_{2A} antagonists in eliciting food intake from this amygdalar site.

β -ENDORPHIN PEPTIDE DERIVATIVES SUPPRESS ALCOHOL INTAKE IN THE N. ACCUMBENS OF P RATS. Resch, G.E.; Simpson, C.W. School of Biological Sciences and Department of Basic Medical Sciences, Univ. Missouri Kansas City, MO 64108. It has been proposed that β -endorphin modulates alcohol consumption at the nucleus accumbens (NAC), an important site in the reward circuit. Like naloxone, peptide fragments of β -endorphin processing (i.e. glycyl-glutamine (Gly-Gln) and β -endorphin(1-27)), injected icv also blocked ethanol drinking. Thus we hypothesized that Gly-Gln and related peptide fragments injected into NAC would also reduce alcohol intake. Using a 24 hr, 2 bottle protocol, rats were supplied with their preferred concentration of ethanol and 24 h measurements of ethanol, water, food, and body weight were recorded for 3 days before and after injection of Gly-Gln(100 nmol) bilaterally into the NAC. Results show Gly-Gln vs saline significantly ($P < 0.0002$) suppressed alcohol intake from a mean of 6.94 ± 1.1 g/kg to 3.5 ± 0.89 g/kg (mean \pm SEM) in the day after injections. Unilateral vs bilateral Gly-Gln was half as effective. Similar data resulted from injections of β -endorphin(1-27). Combined Gly-Gln/ β -endorphin(1-27) injections decreased alcohol intake but showed no additivity. During the days after injections of antagonists, food, water, and body weight did not change. Comparison of Gly-Gln with naloxone show similar suppression of ethanol intake. These data demonstrate that the β -endorphin antagonist peptides derived from processing β -endorphin(1-31) in vivo, i.e. Gly-Gln and β -endorphin(1-27), suppress ethanol intake when injected into the NAC. Supported in part by the Sara Morrison Bequest, UMKC School of Medicine.

EFFECTS OF MERCAPTOACETATE ON DIET CHOICE IN JUVENILE RATS. Swithers, S.E.; McCurley, M.A. Dept. Psychological Sciences. Purdue University, West Lafayette, IN 47907 USA. In preweanling rats, administration of mercaptoacetate (MA) produces physiological changes consistent with blockade of fatty acid oxidation, and decreases the latency of pups to initiate food intake independent of the dam. Further, in adult rats, administration of MA stimulates food intake. However, in peri-weanling rats, administration of MA results in suppression of independent ingestion. It is unclear which mechanisms result in suppression of intake in peri-weanling rats and which mechanisms underlie developmental differences in ingestive responding across rats of varying ages. In the present experiment, we examined the influence of test diet on the effects of administration of MA in juvenile rats past the weaning age, 25 or 30 days of age. Rats were injected with 0 or 68.4 mg/kg MA, and given cups containing either powdered rat chow or a commercial half-and-half milk diet. Cups were weighed after 30, 60, 120 and 240 min to determine intake. Intake of both diets was stimulated by MA during the first 30 minutes. However, during the second 30 min period, intake of the milk diet not affected by MA, while intake of chow continued to be stimulated. By the end of the 240 min test, intake of the milk diet was significantly suppressed by administration of MA. These results suggest that the postingestive consequences of consuming the milk diet following administration of MA result in suppression of intake. Further, differences in behavioral responses to

administration of MA in animals of varying ages may result from differences in diets used for testing.

3:45-5:45 Symposium 3: *Animals models of depression: Recent findings.*

BEHAVIORAL AND PHYSIOLOGICAL RESPONSES TO CHRONIC MILD STRESSORS: GENDER AND STRAIN DIFFERENCES. Bielajew, C., Konkle, A.T.M., Kentner, A.C., & Baker, S.L. School of Psychology, Behavioural Neuroscience Program, University of Ottawa, Ottawa, Canada, K1N 6N5. The results of a series of experiments describing the consequences of chronic mild stressors on a variety of measures in male and female Sprague-Dawley and Long Evans rats are reviewed. Brain stimulation reward thresholds and sucrose intake and preference were tracked to evaluate changes in hedonic status. At regular intervals, body weight and food intake were monitored as was estrous phase in the female rats. Spleen and adrenal weight and plasma corticosterone levels were determined at sacrifice. Overall, behavioral effects associated with chronic mild stressors were generally negligible. Thresholds for brain stimulation reward which were determined twice weekly for several weeks before and during the six weeks of chronic mild stress were unchanged; maximum rates of bar pressing, used as a performance index, were likewise unaltered by the stress experience. Of the sucrose measures (one and 24 hour intake and preference), only the 24 hour intake showed a modest decrease during the stress period, more so in female than in male rats. In contrast, the procedure produced significant alterations in most physiological measures in a strain and gender dependent manner. Rate of weight gain was systematically reduced in most stress groups (especially obvious in males) and corticosterone levels were elevated following both three and six weeks of stressors. The estrus cycle was disrupted soon after the introduction of the chronic mild stressors, in that most animals became acyclic for the duration of the study; this effect was most prominent in the Long Evans strain. We conclude that while physiological disturbances appear as a consequence of exposure to chronic mild stressors, the behavioral tests reveal no evidence of a change in hedonic status.

DRUG WITHDRAWAL AS AN ANIMAL MODEL OF DEPRESSION. Markou, A. Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA 92037, U.S.A. Drug withdrawal in humans is associated with a syndrome reminiscent of a non-drug-induced major depressive episode. In rats, withdrawal from a variety of drugs of abuse, including amphetamine and nicotine, results in elevations in brain reward thresholds reflecting "diminished interest or pleasure" in the rewarding electrical stimuli (i.e., anhedonia). Treatment with a serotonergic antidepressant drug combination involving the co-administration of a selective serotonin reuptake inhibitor (fluoxetine or paroxetine) and a serotonin-1A receptor antagonist reversed the elevations in brain reward thresholds associated with nicotine and/or amphetamine withdrawal, while having no effect on the somatic signs of nicotine withdrawal. Further, the atypical antidepressant bupropion that inhibits the reuptake of dopamine and norepinephrine and acts as antagonist at nicotinic acetylcholine receptors dose-dependently reversed both the reward threshold elevations and the somatic signs of nicotine withdrawal. The reversal of the reward deficits associated with drug withdrawal by clinically proven antidepressant drug treatments suggests that common neurobiological substrates, involving decreased monoaminergic neurotransmission, mediate the symptom of anhedonia characterizing drug- and non-drug-induced depressions. Finally, withdrawal from chronic amphetamine administration led to increased immobility (depression-like behavior) in two other models of antidepressant activity, the forced swim test in the rat and the tail suspension test in the mouse. In conclusion, taken all together these data suggest that there are common neurobiological abnormalities in drug- and non-drug-induced depressions indicating that drug-withdrawal may be a useful rat model for the investigation of the neurobiology of depression in experimental animals.

EARLY DEPRIVATION IN MARMOSSET MONKEYS AND RATS AS ANIMAL MODELS OF DEPRESSION: LONG-TERM NEUROBEHAVIOURAL EFFECTS. Pryce, C.R.; Dettling, A.C.; Rüedi-Bettschen, D; Feldon, J. Behavioural Neurobiology Laboratory, Swiss Federal Institute of Technology Zurich, Schorenstrasse 16, CH-8603 Schwerzenbach, Switzerland. The human epidemiological and clinical evidence is that early life stress, including neglect, abuse and parental loss, markedly increases the likelihood of long-term development of stress-related disorders, including posttraumatic stress disorder and depression. Studies in marmoset monkeys and rats are providing evidence that early life stress in the form of controlled intermittent social deprivation in the postnatal period (early deprivation, ED) leads to chronically altered physiological and behavioural (1) basal status and (2) responsiveness to environmental challenge. In ED marmosets, studied as juveniles to sub-adulthoods, urinary basal cortisol levels were reduced and noradrenaline levels increased. Basal blood pressure, as measured using telemetry, was increased. Social behaviour was reduced in the home cage and in a novel environment. Emotional processing of palatable reward was disrupted: ED marmosets responded less in a progressive ratio schedule indicating reduced motivation (anhedonia) and made more errors when the stimulus-reinforcer relationship was reversed in a visual discrimination task. In Wistar rats, ED adults responded less in a progressive ratio schedule indicating reduced motivation. They demonstrated reduced mobility during the test phase, specifically, of the forced swim test, suggesting reduced coping ability. In Fischer rats, ED adults demonstrated a deficit in escape behaviour in two-way active avoidance following pre-exposure to the mild footshock unconditioned stimulus, again suggesting reduced

coping ability. Also in Fischer rats, ED adults demonstrated attenuation of the basal ACTH circadian profile and attenuation of the corticosterone response to restraint stress. They exhibited increased hypertension when exposed to a novel environment, as measured using telemetry. Expansion of this promising comparative rodent-primate approach to include neurobiological and pharmacological studies will enable us to establish the validity of the chronic effects of ED as an animal model of stress-related disorders including depression and those disorders with which it is commonly co-morbid. Supported by the Swiss National Science Foundation (31-55618.98) and the Swiss Federal Institute of Technology Zurich (TH-24./99)

MURINE MODELS OF DEPRESSION: UTILITY FOR KNOCKOUT AND TRANSGENIC BEHAVIORAL STUDIES. Cryan, J.F. Nervous System Research, Novartis Pharma AG, Basel CH-4002, Switzerland. There has been an upsurge in the development of mice with genetically altered expression of a specific protein, be it a receptor, transporter, enzyme or signal transduction protein. These new tools have the potential to examine novel targets for antidepressant activity for which there are few established pharmacological tools. Further, such strategies can also be employed to investigate the role of specific proteins in mediating the effects of known antidepressants. The majority of studies use simple tests such as the forced swim test or tail suspension test to elucidate their behavioral changes. Such analyses has been used to characterize the effects of mice lacking neurotransmitters e.g. norepinephrine, receptors e.g. mGluR7 and transcription factors e.g. CREB. Other physiological analyses such as tests for locomotor activity, pain sensitivity or cognition might be necessary to implicate behavioral changes to stress-induced depression in various genetically modified mice. The ability to restore, albeit transiently, the phenotype in noradrenaline-deficient mice by administering the synthetic precursor L-deoxyphenylserine is a novel way to confirm that the phenotype is related to noradrenaline function as opposed to adaptive changes resulting from being reared without this monoamine. Much emphasis is being placed on studying individual strain differences in both baseline behavior and in the response to psychotropic medications in mice. In almost all behavioral models, substantial strain differences have been observed. Further analyses of both inbred and outbred strains might help reveal phenotypic behavioral differences that might have an underlying genetic basis relevant to antidepressant action.

DOMINANT AND SUBMISSIVE BEHAVIOR AS A MODEL OF MANIA AND DEPRESSION. ^{1,2}Malatynska, E.; ¹Crites, G.; ¹Rapp, R.; ²Crooke, J.; ²Rosenthal, D.; ²Milewski, M.; ²Brenneman, D. ¹Indiana University School of Medicine, Dept. Pharmacol. & Toxicol. Evansville, IN 47712; ²JNJ Pharmaceutical R&D, Spring House, PA 19477 USA. Bipolar disorder is a mood illness with the two opposite poles of melancholia (depression) and mania. These two opposite states of mood can exist at different times in one individual or can shift toward one pole with variable efficacy. The distribution of dominant-submissive behavior in rats as defined in a competition test has similarities to bipolar affective disorder. Thus, we hypothesized that submissiveness can serve as a model of depression and dominance can serve as a model of mania. Anti-manic drugs decreased dominance and antidepressant drugs reduced submissiveness in our test which, measures the relative success of two food-restricted rats to gain access to a feeder. Rats were randomly paired and placed in an apparatus allowing them to compete for a food reward. The dominant-submissive relationship developed over a two-week period and remained stable for at least the next five weeks. Treatment of the submissive subject for three weeks with imipramine, desipramine or fluoxetine significantly and dose-dependently (fluoxetine) reduced submissive behavior. The effect was attenuated after cessation of treatment with desipramine. Treatments of submissive rats with diazepam (anxiolytic) or amphetamine (psychostimulant) were ineffective. In an independent experiment, dominant rats were treated with drugs commonly used to alleviate mania in the clinic. These included lithium chloride, sodium valproate, carbamazepine and clonidine. We have shown that all of these drugs significantly reduced dominant behavior of rats measured in the competition test. The onset of this effect for all drugs tested was similar to the onset of their therapeutic effect. We conclude that submissive behavior was selectively reduced by antidepressants. Dominant behavior was sensitive to a range of drugs used to treat mania in humans. These studies support the validity of dominant behavior as a model of mania and submissive behavior as a model of depression.

6:00-8:00 Poster Session II: Topics: Anxiety and Stress, Sexual Behavior, Developmental Psychobiology, Neurotransmission, Alcohol, Nicotine and Behavioral Genetics.

41. INVOLVEMENT OF NEUROTRANSMITTERS IN THE ANXIOLYTIC ACTION OF PACAP 38 IN RATS. Telegdy G.; Adamik, A. Dept. Pathophysiology, Neurohumoral Res. Group. Hungarian Academy of Sciences. University of Szeged, Hungary. The action of PACAP 38 was studied in an elevated plus maze for measuring anxiogenic/anxiolytic action in rats. The PACAP 38 was administered into the lateral brain ventricle and the behavior was measured 30 min later. The possible involvement of transmitters was measured by pretreating the animals with receptor blockers which per se did not influence the task, however in the doses used were effective with other neuropeptides. The following receptor blockers were tested: haloperidol, phenoxybenzamine, propranolol, bicuculline, methysergide, atropine, naloxone, PACAP 6-38, and nitro-arginine by blocking nitric oxide synthase enzyme. The following parameters were measured: Total entries into the arms, entries to open

arms/total entries, time spent in open arms/time spent in total entries. Total entries and entries into open arms/total entries were not altered significantly either by PACAP 38 or by receptor blockers. However PACAP 38 increased the time spent in open arms/time spent in total entries. Pretreatment with atropine and bicuculline did not influence the action of PACAP 38 on time spent in open arms. The following receptor blockers diminished the action of PACAP 38: haloperidol, phenoxybenzamine, propranolol, methysergide, naloxone, PACAP 6-38, nitro-arginine. The results demonstrate that in the axiolytic action of PACAP 38 number of transmitters are involved.

42. INHIBITION OF CORTICOSTERONE WITH METYRAPONE DELAYS EXTINCTION OF THE CONDITIONED EMOTIONAL RESPONSE (CER). Hernández-Poudevida, P.; McEwen, B.S.; Quirk, G.J. Dept of Physiology, Ponce School of Medicine, Ponce, Puerto Rico 00732, and Rockefeller University, NY, NY 10021. Posttraumatic stress disorder (PTSD) is not an inevitable consequence of trauma. It has been suggested that low levels of cortisol following a traumatic experience may be a predisposing factor for PTSD (Yehuda et al., 1998). It has also been suggested that PTSD may be due to deficits in extinction of conditioned fear (Gorman et al., 2000). Could corticosteroids be involved in extinction learning? We addressed this in rats with the corticosterone synthesis inhibitor metyrapone. On day 1, rats received 7 tones paired with footshock (0.5 mA). On day 2, rats were injected with metyrapone (25mg/kg n=17 or 50mg/kg n=17, s.c) or vehicle 90 min prior to 15 extinction tones. On day 3, recall of extinction learning was assessed. Metyrapone treated rats showed normal expression of freezing and suppression of bar pressing for food (CER) at the start of extinction. Rats that received the higher dose of metyrapone were delayed in their within-session extinction of suppression. On day 3, half of the metyrapone rats in the high dose group remained completely suppressed to the tone, compared to only one of the vehicle rats (fisher exact test, $p < 0.01$). Metyrapone did not alter spontaneous press rates, suggesting no locomotor deficit. Our findings suggest that stress-induced elevations of corticosteroids are necessary for normal extinction of conditioned fear. Low levels of cortisol may predispose individuals to develop PTSD, perhaps by compromising extinction learning. Supported by a BRIN Fellowship.

43. LONG TERM MEMORY FOR EXTINCTION OF AUDITORY FEAR CONDITIONING REQUIRES PROTEIN. Santini, E.; Quirk, G.J. Dept of Physiology, Ponce School of Medicine, Ponce, Puerto Rico 00732. Rather than erase conditioning, extinction of conditioned fear is thought to form a new memory. We recently showed that NMDA receptors are required for long-term but not short-term memory for extinction of auditory fear conditioning (Santini et al., 2001). Is protein synthesis also involved in long-term extinction memory? It has been reported that extinction of inhibitory avoidance (Vianna et al., 2001) and conditioned taste aversion (Berman & Dudai, 2001) require protein synthesis while extinction of context fear conditioning does not (Lattal & Abel, 2001). We examined the effect of intraventricular infusions of the protein synthesis inhibitor anisomycin on short- and long-term extinction of auditory fear conditioning. On day 1, rats received 7 tones paired with footshock. On day 2, rats received 15 extinction tones in the presence of anisomycin (300 ig icv) or ACSF. On day 3, recall of extinction was assessed. Aniso did not alter expression of freezing (72%) or within-session extinction of freezing (12%). 24-hrs later, however, aniso-treated rats showed high fear to the tone, rebounding to 82% of acquired freezing, compared to only 38% in controls ($t=2.1$, $df=18$, $p < 0.05$). The high rebound of fear in the aniso-treated rats suggests amnesia for extinction memory. In further support of this, aniso-treated rats showed no savings in their rate of re-extinction. These findings suggest that, similar to other forms of learning, long-term memory for fear extinction involves NMDA-mediated calcium entry and subsequent events that lead to the synthesis of new proteins. We are currently using microcannulation techniques to determine the site of extinction-induced protein synthesis. Supported by R29-MH58883, S06GM08236.

44. STIMULATION OF INFRALIMBIC CORTEX SIMULATES FEAR EXTINCTION. Vidal-Gonzalez, I.; Milad, M. R.; Quirk, G. J. Dept. of Physiology. Ponce School of Medicine, Ponce, P.R 00732. Neuronal recording in the medial prefrontal cortex, specifically in the infralimbic cortex (IL), during auditory fear conditioning revealed that IL neurons signal the tone only during the recall of extinction (Milad & Quirk, Nature 2002), suggesting that IL neurons may store extinction memory. Pairing electrical stimulation with conditioned tones (100 Hz, 100-300 ms after tone onset) caused a significant reduction in freezing to the tone. It remains unclear, however, if stimulation reduced freezing by mimicking naturally occurring tone responses. To address this, we varied temporal and anatomical parameters. On day 1 rats received 5 tones (30 sec) paired with footshock. On day 2 rats received 8 extinction tones, each with a brief electrical stimulation in either IL or adjacent prelimbic area (PL). Stimulation of PL had no effect on freezing levels (88%) when compared to unstimulated control rats (87%). Stimulation of IL at 20 Hz, which more closely approximates actual IL firing rates, was as effective as 100 Hz (20 Hz: 47%, 100 Hz: 56%). We also varied the time at which IL stimulation was given relative to tone onset (-1.0s, +0.1s or +1.0s). Only stimulation given at 100 ms after tone onset (the actual latency of IL tone responses) significantly reduced freezing. These data suggest that electrical stimulation reduces conditioned freezing because it mimics a naturally occurring safety signal induced by extinction training. Stimulation of mPFC might be used clinically to strengthen extinction memory in patients suffering from anxiety disorders. Supported by: NIH grants F31- MH12818, MH58883,

45. THE VENTROMEDIAL PREFRONTAL CORTEX IS NECESSARY FOR THE RAPID CONSOLIDATION OF EXTINCTION LEARNING. Lebron, K.; Quirk, G.J. Dept. of Physiology, Ponce School of Medicine, Ponce, Puerto Rico 00732. Extinction of conditioned fear is thought to involve the formation of a new memory (memory of safety) instead of the erasure of the conditioning memory (memory of fear). We previously reported that lesions of the ventromedial prefrontal cortex (vmPFC) did not prevent extinction within a session, but blocked recall of extinction 24hrs later, suggesting a role of vmPFC in consolidation of extinction learning (Quirk et al., 2000). To investigate if this deficit was permanent, vmPFC lesioned (n= 11) and sham (n= 11) rats were exposed to fear conditioning (7 tone-shock trials) and extinction (15 tone alone trials) on day 1 (as in our previous study). Then, on days 2 to 7 rats received 2 extinction trials to test for recall of extinction memory. Compared to shams, vmPFC lesioned rats showed normal extinction on day 1, but full recovery of freezing on day 2 (sham: 51%, lesion: 100%, $p < .05$), replicating our earlier findings. Furthermore, high recovery of freezing was also observed on days 3-4 in vmPFC lesioned rats, indicating that the deficit in extinction memory persisted. However, there was no significant difference between groups by day 5. In fact, vmPFC lesioned rats re-extinguished at a faster rate from days 2 to 7 than vmPFC lesioned rats that never received extinction on day 1. These findings suggest that vmPFC lesioned rats could recall original extinction training if given sufficient retraining. In conclusion, while vmPFC is not the only site of extinction learning, it appears to enable a rapid consolidation of extinction, consistent with a role of the PFC in maximizing behavioral flexibility.

46. CRF INCREASES STARTLE BUT NOT FEAR POTENTIATED STARTLE IN MICE Risbrough, V.B.; Geyer, M.A. Dept. of Neurosciences, UCSD, La Jolla, CA 92093 USA. The fear-potentiated startle (FPS) model of anxiety in rodents has face, predictive, and construct validity for fear responding in humans. FPS is a phenomenon in which subjects are classically conditioned to associate a conditioned stimulus (CS) with a noxious unconditioned stimulus (US). Post-conditioning, subjects exhibit exaggerated acoustic startle responses (ASR) in the presence of the CS, indicating a "fearful" conditioned response. Corticotropin releasing factor (CRF), a neuropeptide released during conditions of threat, increases unconditioned fear and anxiety-like behaviors in rodents. Moreover, CRF antagonists block FPS and fear-conditioned freezing in rats, indicating a potential role for CRF receptors in learned fear responses. Using two strains of mice with different levels of expression of FPS, we sought to determine if CRF receptor activation could intensify learned fear responding after FPS training, suggesting a role for CRF in the expression of FPS. Mice were trained using a 30-sec light CS and a 0.14-mA footshock US 24-hours before testing. CRF (0.1-1.0 μ g, ICV) was administered 1-hour before FPS testing in 129SvEv (poor FPS) and DBA/1J mice (good FPS). In both strains, CRF increased overall ASR (with and without the CS present) at all doses tested, consistent with previous reports in untrained rats and mice. On a percentage basis, FPS was unaffected by CRF in DBA/1J mice, however FPS was reduced in 129SvEv mice. These results are consistent with the effects of CRF on amygdala-independent ASR and replicate previous reports of CRF-induced deficits in cognitive performance. We conclude that the putative CRF receptors involved in FPS are most likely at saturation, and that further activation of CRF receptors results in increases in unlearned fear or anxiety and disruption of mnemonic processes.

47. KINDLING INDUCED LASTING INTERICTAL ALTERATIONS OF AFFECTIVE BEHAVIOR. Adamec, R.E. Dept. of Psychology, Memorial University, St. John's, NL, A1B3X9, Canada. Kindling of the mammalian limbic system has been suggested as a model of epileptogenesis in complex partial seizure disorder (CPS). The most commonly agreed upon problems of an affective nature associated with epilepsy are anxiety and depression. An extensive literature implicates the amygdala as well as structures afferent and efferent to the amygdala in the production of fearful and anxiety related states in animals and humans. It is of interest, then, that anterior temporal lobectomy resecting amygdala and anterior hippocampus in human epileptics reduces a preexisting anxiety disorder. Since most definitions of anxiety in the DSM-IV contain an element of fear, study of the neural substrates of fear, and in particular amygdala circuitry, should yield insights into the substrates of anxiety. Study of the impact of experimental epilepsy on these substrates may also provide useful information on the etiology of anxiety associated with epilepsy. Kindling of the amygdala and hippocampal system in rodents and felines has produced long lasting interictal increases in defensive and anxiety-like behavior (ALB). Effects lasting up to two months in rodents and nearly 4 months in cats have been observed. Most recent data suggest long term potentiation in selected amygdala efferents in the right hemisphere are critical mediators of lasting increases in feline defensive behavior. Work in cats has identified hemisphere as an important factor in neural mechanism of kindling induced behavioral change. The work also suggests that long term potentiation (LTP) in particular neural circuits is responsible for particular behavioral changes following kindling. Continuing work in rodents in this lab is guided by hypotheses derived from cat work. A recent meta analysis of the literature on kindling and behavior has suggested a number of factors that may be involved in determining behavioral outcome of limbic kindling in rodents. Included among these are: extent of kindling; strain of rat kindled; premorbid affective state; limbic focus location; LTP in particular limbic circuits. This poster will describe these factors and research guided by them. It will also share initial findings of studies

investigating the role of LTP in behavioral change in felines and rodents.

48. CENTRAL INFUSION OF AN ANABOLIC STEROID INDUCES MODULATION OF AFFECTIVE COMPONENTS OF BEHAVIOR. Rivera, J.C.¹; Fernandez, M.¹; Delgado, C.¹; and Jorge, J.C.² Department of Biology¹, Río Piedras Campus, Department of Anatomy², Medical Sciences Campus, University of Puerto Rico San Juan-P.R. 00936. The androgen 17 α -methyltestosterone (17 α -meT) is one of the most commonly abused anabolic androgenic steroids (AAS) despite its adverse effects in affective components of behavior. We wanted to determine the behavioral effects of AAS after bilateral infusion of this compound into the dorsomedial hypothalamus (DMH, coordinates DV 8.6, AP -2.8) in gonadally-intact female rats (n= 33). Control animals were infused with 0.9% saline whereas experimental animals were infused with 17 α -meT (1 μ M) (0.5 μ l/side) 5 minutes before each behavioral test. The Conditioned Place Preference (CPP) and the Vogel Conflict Test were employed. In addition, exploratory and locomotor behaviors were assessed with activity chambers. We found that AAS have aversive properties in the CPP ($p \leq 2.11 \times 10^{-6}$). This effect was associated with a decrease in rearing ($p \leq 5.1 \times 10^{-5}$) and locomotor activity ($p \leq 0.02$). In addition, AAS-infused animals showed a longer latency to consume water after punishment when compared to controls ($p \leq 0.03$). Our data shows that central infusion of 17 α -meT into the DMH produces aversive and anxiogenic effects. We hypothesize that GABA_A-receptors mediate these modulatory effects on behavior. JCR was supported by NIH-BRIN award (P20RR16470). Study supported by NIH-COBRE (RR15565), NIH-BRIN (RR16470), and RCMI-MS (RR03051) to JCJ.

49. IMPAIRED EPISODIC OBJECT MEMORY AND INCREASED ANXIETY IN HDC KNOCKOUT MICE. De Souza Silva, M.A.¹; Dere, E.¹; Topic, B.¹; Spieler R.E.²; Haas H.L.^{1*}; Huston, J.P.¹ ¹Institute of Physiological Psychology, and ^{1*}Institute of Neurophysiology, Center for Biological and Medical Research, Heinrich-Heine-University, D-40225, Duesseldorf, Germany. ²Oceanographic Center, Nova South-eastern University, Dania, FL, USA. Histamine has been implicated in a variety of physiological and behavioral functions. We investigated some behavioural and neurochemical phenotypes of mice, which are deficient for the HDC gene, and, thus, cannot synthesize histamine from its precursor histidine. The HDC^{-/-} mice showed reduced exploratory activity in small and large-sized open-fields, as well as in an 8-arm maze. The H1 receptor antagonist pyrilamine dose-dependently reduced rearings in the controls, but not in HDC^{-/-} mice. In the rotarod-test HDC^{-/-} mice performed superior to the controls. In two separate measures of unconditioned anxiety HDC^{-/-} mice behaved more anxious than controls. During the two days of object exploration with four equivalent objects the HDC^{-/-} mice showed fewer contacts but no indication of impaired object recognition. However, the HDC^{-/-} mice were strongly impaired when they had to discriminate different objects varying with respect to their familiarity; that is, in dependence of the number of previous encounters with specific objects. Biochemical assessments revealed that the HDC^{-/-} mice had increased acetylcholine concentrations in the frontal cortex and neostriatum. Furthermore, the HDC^{-/-} mice had higher DOPAC concentrations in the neostriatum and cerebellum, increased DOPAC/DA ratios in the neostriatum and ventral striatum and higher 5-HIAA/5-HT ratios in the frontal cortex relative to the controls. These results suggest an important role of brain histamine in exploratory behaviors, anxiety, object memory and brain neurotransmitter homeostasis. Supported by the Deutsche Forschungsgemeinschaft.

50. ESTROGEN MODULATES THE HEDONIC AND ANTI-ANXIETY PROPERTIES OF THE NEUROSTEROID 3 α DIOL. Marrero, J.¹; Lorenzini, I.¹; García-Corbea, E.²; Serrano, G.³; Jorge, JC³. Departments of Biology¹ and Chemistry², Río Piedras Campus, Department of Anatomy³, Medical Sciences Campus, University of Puerto Rico, San Juan, P.R. 00936. The neurosteroid 3 α -androstanediol (3 α DIOL) is an endogenous testosterone metabolite. It has been proposed that 3 α DIOL mediates the anxiolytic and rewarding effects of androgens in males. We wanted to extend this proposition by studying females. Half of the females received subcutaneous 5mm Silastic® tubing implants filled estradiol benzoate (OVX+EB) and the other half received empty implants (OVX). The conditioned place preference (CPP) and elevated plus maze (EPM) tests were employed. On day 0, animals were allowed to choose the preferred compartment of an activity chamber with light/dark enclosures. Experimental animals were injected (i.p.) with either 0.9% saline + 30% β - cyclodextrin (vehicle) on the preferred side or 1mg/kg 3 α DIOL in the non-preferred side in alternating days for 10 days. Control animals were injected with vehicle throughout CPP. On day 11, drug-free animals were allowed to choose its preferred side. Two days after CPP, anxiety was monitored with an automated EPM after a single 3 α DIOL injection. We found that 3 α DIOL induced CPP in OVX ($p \leq 0.05$) but not OVX+EB animals. In addition, this neurosteroid induced an increase in open arm entries ($p \leq 0.01$) and an increased % time in the open arms ($p \leq 0.04$) of the EPM in OVX females but not OVX + EB females. These effects were not associated with changes in locomotor activity. We conclude that estrogen modulates the hedonic and anti-anxiety properties of 3 α DIOL in females. Funding provided by NIH-BRIN (RR16470) to JMR and ILL, and MBRS-RISE (R25GM61838) to EGC. Study supported by NIH-COBRE (15565), NIH-BRIN (RR16470) and RCMI-MS (RR 03051) to JCJ.

51. MODULATORY EFFECTS OF ESTROGEN ON ANXIETY RELATED BEHAVIORS. Lizardi, L. and Jorge, J.C. School of Science, Math. and Tech., Universidad del Este-AGMUS, Dept. of Anatomy, Medical Sciences Campus, University of Puerto Rico. It has been argued that there are robust sex-specific differences in affective components of behavior. The purpose of this study was to determine if endogenous fluctuations of sex hormones alter behavior. Moreover, we want to assess the role of estrogen in modulating anxiety-related behaviors. Sprague Dawley female rats were followed through three consecutive estrous cycles. Those cycling normally (n=33) were subjected to either the Vogel Conflict Test (VCT) or the Elevated Plus Maze (EPM). Afterwards, animals were ovariectomized, half received an empty 5 mm silastic tubing implant (OVX), and half received an implant filled with estradiol benzoate (OVX-E). A week after recovery, animals were tested in the VCT or EPM in a counterbalanced fashion. Analysis was done according to cycle stage and to the status of estrogen replacement. We found that OVX-E animals displayed a greater number of licks ($t = -4.46$, $P \leq 0.001$) and shocks ($t = -4.16$, $P \leq 0.001$) accompanied by an increase in the latency after punishment ($t = -2.69$, $P \leq 0.02$) when compared to OVX animals. Analysis of naturally cycling females showed a tendency to an increased latency in late proestrous to estrous females when compared to diestrous females. Estrogen replacement or natural fluctuations in gonadal steroids had no effect on EPM behavior. Therefore, estrogen seems to modulate anxiety responses in VCT. Experiments are underway to determine if these behavioral changes correlate with extinction of fear conditioning in females. (L.L. supported by UE-AGMUS, and J.C.J. by NIH-COBRE (15565) and NIH-BRIN (RR16470)).

52. ACTIVITY-STRESS MODIFIES HIPPOCAMPAL MORPHOLOGY AND LOCUS COERULEUS FOS-IMMUNOREACTIVITY. Lin, S.M.; Gasper, E.R.; Campbell, T.; *Kinsley, C.H.; & Lambert, K.G. Dept. of Psychology, Randolph-Macon College, Ashland, VA 23005; *Dept. of Psychology, University of Richmond, Richmond, VA 23173. Because chronic stress has been shown to compromise hippocampal morphology and cellular functions (Fuchs et al., 2001; Magarinos, Verdugo & McEwen, 1997), it is important to investigate the effects of various types of stressors on this brain structure so critical for survival. In the current study, activity-stress (A-S), a stressor involving housing food-restricted animals in cages with attached running wheels, was used as an ecologically relevant chronic stressor. In addition to hippocampal morphology and apoptosis, cellular activity in the locus coeruleus was assessed due to its intricate ties with the stress response system (Bockstaele, Bajic, Proudfit, & Valentino, 2001; Dent, Smith, & Levine, 2001). The following groups were used: *A-S group* (n=6), in which animals lived in activity cages and were fed for 1.5 hrs per day; an *Active-Control (A-C) group* (n=6) in which animals lived in activity cages with no food-restriction regime; and a *Pair-Fed (P-F) control group* (n=6), in which animals lived in standard cages but were food-yoked to A-S animals. Following four days of A-S, all groups were sacrificed and the brains were prepared for immunohistochemistry; specifically, the hippocampal tissue was assessed for caspase-3 immunoreactivity and the locus coeruleus was assessed for *c-fos*-immunoreactivity. Light microscopy analysis revealed no effect of four days of A-S on apoptosis (as measured by caspase-3); however, the width of CA1, CA3, and dentate gyrus cell body bands were significantly smaller in A-S animals. Additionally, A-S animals had fewer *fos*-immunoreactive cells in the locus coeruleus following this intense chronic stress. Thus, evidence of hippocampal and locus coeruleus modifications after just four days of chronic stress support prior observations (e.g., Lambert et al., 1998) of significant stress-induced brain plasticity.

53. CONDITIONED PLACE PREFERENCE IN NON COPULATING MALE RATS. Wendy, Portillo; Francisco J, Camacho and Raúl G, Paredes. Instituto de Neurobiología UNAM, Juriquilla, Querétaro. México, 76001. Approximately 10% of male rats fail to initiate copulation, even if they are repeatedly tested with receptive females. These animals are called “noncopulators” (NC). In the present study we evaluated if NC male rats could develop conditioned place preference (CPP) to a morphine injection (1mg/kg). CPP evaluates if the animals are able to associate a reward state with a particular environment. This would allow us to determine if the NC rats have a functional general reward system. In addition, we evaluated if the NC male rats have motor alterations that could interfere with CPP. Male Wistar rats were classified as copulating if they mated in four tests (C), and NC if they did not execute any pattern of sexual behavior in any of the tests. No alterations in motor coordination, as evaluated by a rotarod, were found. A clear CPP was developed after morphine injection in C and NC rats. No change in preference was observed in saline treated animals. These results suggest that NC rats have a functional general reward system and together with previous results from our laboratory indicate that NC rats have a reduced sexual motivation. Supported by DGAPA IN227402 and CONACyT

54. SYNERGISTIC ACTIONS BETWEEN MATING AND CHEMICAL STIMULATION OF THE MEDIAL AMYGDALA (MEAPD): TOWARDS THE FORMATION OF A NEUROENDOCRINE MEMORY. Lehmann, M.L. and Erskine, M.S. Boston University Boston, MA 02215 USA. The medial amygdala is uniquely responsive to spaced mating stimulation and plays an integral role in initiating mating-induced neuroendocrine memory formation. Our lab has demonstrated that temporally spaced chemical activation of the MEAPd with three infusions of an excitatory amino acid solution (EAA; Asp/Glu/Gly -10 μ M/5 μ M/1 μ M) or multiple intromissions (>10) from males induce pseudopregnancy (PSP). Single EAA infusions or low numbers of intromissions (<5) have no effect on estrus cyclicity and thus are considered sub-threshold for PSP establishment. In the present investigation we examined the

influence of a sub-threshold EAA pretreatment in the MEApd on PSP induction when the chemical stimulus was coupled with sub-threshold mating stimulation. Proestrus females with unilateral cannulas directed at the MEApd were infused with 0.4 μ l of either EAA or PBS. 30 min later females were mated with a sexually active male until 5 intromissions were received. Vaginal smears were used to determine estrous cycle regularity and PSP occurrence. Pretreatment with EAA significantly enhanced the sub-threshold mating treatment by initiating PSP in 83% (5/6) of females compared to control PBS pretreated females (0/6) ($p < 0.05$). The results show strong synergistic effects between direct glutamate stimulation of the MEApd and mating stimulation. This provides strong *in vivo* evidence to support the hypothesis that glutamate release occurs in response to intromissions which are responsible for PSP initiation. Supported by MH01435 and MH64187 to MSE.

55. EXPRESSION OF THE FEMALE SEXUAL BEHAVIOR IN A MULTIPLE CHOICE TEST DURING THE ESTROUS CYCLE OF THE RAT. Ferreira-Nuño A., Morales-Otal A. & Velázquez-Moctezuma J. Área de Neurociencias. Universidad Autónoma Metropolitana-Iztapalapa. In paced mating (when the female is able to control the sexual stimulation received), sexual behavior can be reinforcing. Some motivational aspects of the female sexual behavior (FSB), were evaluated in a multiple choice arena. Four transparent plexiglas cylinders were made and put it together in a cross fashion, forming in the center an additional compartment. In each cylinder, a small hole was made in the bottom, and all the holes were located in the center area. Through these holes only the female could freely move from one compartment to the other. Four sexually active males were selected, from a group of ten males. Also, intact adult females were selected in diestrous by a vaginal smear. Each male were placed in the outer compartments and one female, was introduced in the center chamber with all holes closed, during five minutes, and then, all the holes were opened. The test lasted 15 min. and we recorded the approach latency (AL, latency for the female to enter the male's chamber after the test started). Mount latency (ML, latency from the female's entry into the male's chamber to the first mount). Data of the FSB were analyzed considering the day of estrous as D0, the previous day as D-1, and the following days as D1 and D2. The time spent by the female with each male or in the center chamber were recorded and compared between these four days. In all days registered, the females spent significant more time with one of the four males and this feature increases around the estrus. Not significant differences were observed respect AL, ML.

56. NORADRENERGIC AFFERENTS TO MEDIAL AMYGDALA MODULATE MATING-INDUCED C-FOS EXPRESSION. Carey, P.S.; Erskine, M.S.; Cameron, N. Department of Biology, Boston University, Boston, MA 02215 USA. The A1 and A2 (NTS) noradrenergic cell groups are activated in response to mating and project to the posterodorsal medial amygdala (MePD). To discern the role these cells play in mating-induced c-Fos expression in the forebrain, they were selectively lesioned by the immunotoxin anti-dopamine- β -hydroxylase-saporin (DBH-SAP) 10 days prior to mating. Ovariectomized female rats were given bilateral MePD infusions of either 0.2 μ l (20 ng) DBH-SAP or 0.2 μ l aCSF. Eight days later the animals were given estradiol benzoate (10 μ g sc) followed by progesterone (500 μ g) to induce estrous behavior. They then received one of four mating treatments (home cage, mounts only, 5 intromissions, 15 intromissions) and were perfused 2 hrs later. The forebrains were cut in 30 μ m slices and processed by ICC to visualize Fos-IR (immunoreactive) nuclei. Fos-IR nuclei were counted in the medial preoptic area (mPOA), bed nucleus of the stria terminalis (BNST), paraventricular hypothalamic nucleus (PVN), ventromedial hypothalamus (VMH) and MePD. MePD DBH-SAP infusions decreased the number of DBH-IR cells in A1 and A2 by 20% and 30%, respectively. Fos expression was elevated in both the aCSF and DBH-SAP animals that received mating stimulation. In the BNST, significantly more FOS-IR cells were observed in the DBH-SAP animals than in the aCSF animals, suggesting a possible inhibitory role for the noradrenergic input to this area. There was no significant effect of DBH-SAP on Fos-IR in the other areas examined. Our results show that the noradrenergic cells that innervate the MePD modulate mating-induced activity in downstream sites such as the BNST. Supported by MH64187 and MH01435 to M.S.E.

57. BOTH CHRONIC MILD STRESS AND BRAIN-STIMULATION REWARD INDUCE ESTRUS CYCLE DISRUPTIONS IN THE FEMALE RAT. Konkle, A.T.M.; Baker, S.L.; Kentner, A.C.; Santa-Maria Barbagallo, L.; Bielajew, C. School of Psychology, Behavioural Neuroscience Program, University of Ottawa, Ottawa, Ontario, Canada, K1N 6N5. The chronic mild stress (CMS) procedure has been explored as an animal model of depression; the nature of the stressors is thought to mimic the everyday life difficulties that have been associated with the development of depressive symptomatology in some individuals. The greater incidence of depression in women that is typically reported in the clinical literature prompted us to evaluate the effects of CMS in female subjects. We have previously shown CMS-induced reductions in sucrose intake in the 24h test but in a separate group, we found no such effects on brain stimulation reward (BSR) thresholds. In this study, we evaluated both measures (sucrose and BSR) as a consequence of stress in the same animals and found no correlation between the two results. Generally, BSR thresholds were unchanged and 24h sucrose intake was reduced in both Sprague-Dawley and Long Evans rats. From this as well as previous work, we and others have concluded that the behavioral consequences of CMS are unreliable. However, CMS effects on physiological indices appear to be more dependable. For example, CMS exposure produces estrus cycling irregularities in female rats more greatly so in Long Evans than in Sprague-

Dawley rats. However, the administration of BSR, employed as an index of hedonic change in stress tests, also renders the rats acyclic. We are continuing to monitor the animals' daily estrus phase following the termination of both CMS and BSR testing in order to establish whether cyclicity is regained. These results suggest that both appetitive and aversive stimuli disrupt the estrus cycle; the mechanisms underlying this phenomenon warrant further investigation.

58. CHARACTERIZATION OF 50 KHZ VOCALIZATIONS IN MALE RATS. McGinnis, M.; Vakulenko, M.; Meas, S. Center for Anatomy and Functional Morphology, Mount Sinai Sch. Med. New York, NY 10029 USA. Male rats emit ultrasonic vocalizations in reproductive settings. We developed a method to assess vocalizations using a stimulus rat. The stimulus is placed behind a wire barrier for 5 min, then removed. Vocalizations are then recorded for 5 min. This method provides robust numbers of vocalizations. For the first study, male rats were castrated and tested for the restoration of vocalizations. In one group males were allowed to copulate freely; in the other, females had vaginal masks to prevent intromissions and ejaculations. We found restoration of vocalizations only in males allowed to ejaculate. We also measured vocalizations in sexually naive and sexually experienced males following exposure to either castrated males (cast), testosterone-treated (T) males, ovariectomized females (ovx), or ovx females receiving estrogen plus progesterone (E+P). Males in both groups vocalized significantly more after exposure to E+P females than either cast or T males. However, the sexually experienced males vocalized significantly more after exposure to E+P females than did naive males, and significantly more after exposure to E+P females than ovx females. Our results show that 1) sexual experience facilitates vocalizations in male rats, 2) vocalizations are highest after exposure to a hormonally receptive female, and 3) vocalizations can be used as a sensitive index for assessing the hormonal disposition of conspecifics.

59. ENVIRONMENTAL ENRICHMENT REVERSES SPATIAL LEARNING AND MOLECULAR DEFICITS IN DEVELOPMENTAL LEAD NEUROTOXICITY. Guilarte, T.R.; Toscano, C.D.; McGlothan, J.L.; Weaver, S.A. Department of Environmental Health Sciences, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD. The developing brain is highly susceptible to lead (Pb) exposure and deficits in cognitive function are the principal effects of Pb neurotoxicity. We have previously shown that Pb exposure produces long-term deficits in spatial learning that was associated with reduced expression of the NMDA receptor subunit 1 (NR1) gene in the hippocampus. In the current study, we set out to determine if environmental enrichment was an effective strategy in altering the learning and molecular deficits previously documented in young adult rats (50 days of age) exposed to Pb during development. Control rats or rats exposed to Pb during gestation and lactation until weaning were housed in standard laboratory cages (isolated) or in "enrichment cages". Rats were housed under these conditions from weaning, upon termination of Pb exposure, until the end of spatial learning testing that started at 50 days of age. As previously documented, Pb-exposed rats reared in isolated cages were dramatically impaired in the acquisition of the water maze task relative to all other groups. On the other hand, Pb-exposed rats reared in enrichment cages performed as well as control rats in an enriched environment and better than control-isolated rats. Recovery of learning performance in Pb-exposed enriched rats was associated with induction of BDNF mRNA and reversal of the NR1 subunit mRNA deficits in the hippocampus. These findings demonstrate for the first time that the learning and molecular deficits induced by developmental Pb exposure are reversible by providing a social and stimulating environment. Further, we proposed environmental enrichment as an intervention strategy that is applicable for the treatment of cognitive deficits associated with childhood Pb intoxication. [Supported by NIEHS grant # ES06189 to TRG]

60. THE EFFECT OF A SINGLE VERSUS REPETITIVE PAIN EXPERIENCE DURING INFANCY ON ANXIETY AND SPATIAL LEARNING IN JUVENILE MICE. Stanford L.; Darrah, M; Kelly, C.; Schellinck, H. M. Department of Psychology, Dalhousie University, Halifax, NS Canada B3H 4J1. Exposure to pain during development has long been hypothesized to disrupt behaviour in later life. (Hebb, 1949, Organization of Behaviour). Recent evidence has shown that rats subjected to pain as infants are more anxious as adults (Anand & Scalzo, Bio. Neonate, 77, 2000). In Experiment One, we investigated the influence of early pain experience on anxiety and learning and memory in mice. Neonatal mice were exposed to a one time acute pain, i.e., a tail snip at postnatal day 8 or repetitive pain, i.e., paw pricks on postnatal days 8-14. When tested in an elevated plus maze on Day 30, both acute and chronic pain mice showed behavioural changes indicative of increased anxiety compared with control animals. The effects included a reduction in open arm entries, percent time spent in the open arms and a decrease in head dips. In addition, chronic pain animals showed a greater decrease in time spent in the open arms and in number of entries into the open arms as well as an increase in stretch attends compared with acute pain animals. There were no differences in the number of line crossings in the experimental and control animals. This pattern of results would suggest that the pain exposed animals showed an overall increase in risk assessment, a behaviour associated with hypervigilance in humans. When tested in the Morris Water Maze, these mice demonstrated an intact working memory in a three-day acquisition task as well as in a probe trial and reversal trials. Thus, it appears that their increased anxiety did not adversely affect their performance in a spatial working memory task. In a second experiment, the effect of environmental enrichment on decreasing anxiety in mice experiencing early neonatal pain

was assessed. There was no difference in anxiety between control and experimental animals when tested in the elevated plus maze. The implications of this failure to replicate the results of the initial effect are discussed.

61. SELECTIVE BASAL FOREBRAIN CHOLINERGIC LESIONS ON POSTNATAL DAY 7 HAVE SHORT-TERM EFFECTS ON RAT PUPS' BEHAVIOUR. Scattoni, M.L.; Calamandrei, G.; Puopolo, M.; Ricceri L. Section of Comparative Psychology, Lab. Pathophysiology, Istituto Superiore di Sanità, Rome ITALY. We have previously shown that intracerebroventricular (icv) injections of the selective cholinergic immunotoxin 192 IgG-saporin on postnatal day (pnd) 7 induces behavioural alterations already detectable in the third postnatal week (e.g. avoidance learning impairments on pnd 15, wall rearing inhibition on pnd 18). In the present study we analysed effects of the same icv 192 IgG-saporin injections on pnd 7 upon neonatal behavioural endpoints. Number of ultrasonic vocalizations (UVSs) emitted by 192 IgG-saporin and control rats were recorded on pnds 9, 11 and 13. On pnd 13 rats also underwent a 4-min homing test (an olfactory based test to measure orientation towards home nest material). 192 IgG-saporin reduced the number of USVs at all ages considered, but the effect was more dramatic on pnd 11 and 13. In the homing test no differences emerged between cholinergic lesioned and control pups in time to reach the home nest area and in total locomotor activity (the commonest behavioural parameters considered). In the initial part of the test, however, 192 IgG-saporin pups resulted more active than controls over the nest scented area of the arena. These data suggest that removal of the basal forebrain cholinergic neurons in the first postnatal week modifies rat pup behaviour (reduction of USVs and altered patterns of exploration of the experimental environment), and, likely, mother-pup interactions.

62. EARLY POSTNATAL STRESS AND ADULT BEHAVIORAL TESTING ALTER CORTICAL MORPHOLOGY IN MOUSE. Natasha Jarvis, Kimberly Watson, Carmen Redding and Christine F. Hohmann, Morgan State University, Baltimore, MD 21251 We have previously shown significant, sex dependent alterations of exploratory behavior in mice exposed to neonatal temperature/separation stress. The present study aims to see if these mice also sustain changes in cortical morphogenesis. Between postnatal days [PND] 1 and 7, Balb/CbyJ mice were exposed on alternating days to 30 min. of cold (4, aC) or hot (37, aC) stress or remained with their dams. Weanlings were divided into four groups: Stressed Behavioral (SB), Non-Stressed Behavioral (NSB), Stressed Non-Behavioral (SNB) and Non-Stressed Non-Behavioral (NSNB). At PND 90, SB and NSB mice were tested in an Open Field Object Recognition (OFOR) task and subsequently perfused for histology. Computerized morphometry was performed in sensory-motor cortex on Nissl stained, coronal sections, blind to the origin of the tissue. We found significant, treatment-dependent alterations in cortical widths for total cortex and layers II+III, IV and V. In SB mice, cortical widths decreased in total cortex and layers II/III of both sexes compared to NSB mice and also compared to SNB and NSNB mice. Most decreases were more pronounced in the male. In layer IV of the SB, cortical widths decreased in the male but increased in the female. Cortical widths of NSB animals in all layers and both sexes was equal to or greater than that of the non-behaviorally tested controls (NSNB), except for layer IV where cortical width decreased for both NSB males and females. Thus, we here show significant sex and cortical layer dependent alterations in response to neonatal stress as well interaction between stress and behavioral exposure on cortical morphogenesis. Supported by IP20RR11606, SO6GM51771 and the National Alliance for Autism Research (NAAR).

63. SEX DIFFERENCES IN CONDITIONING AFTER PRENATAL CHOLINE. Brownlee, L.; Washington, K.; Hohmann, C.; Berger-Sweeney, J. Depts. Biology, Wellesley College and Morgan State Univ. USA. Neonatal basal forebrain (BF) lesions on postnatal day (PN)1 have long-term consequences on brain morphology and behavior. In mice, PN1 BF lesions decrease cholinergic markers in neocortical targets and alter the morphogenesis of pyramidal neurons, similar to alterations in Down and Rett Syndromes. In the current study, we examined effects of prenatal choline (a precursor for acetylcholine) supplementation of the mother on BF lesion-induced impairments in mouse offspring. Because the cholinergic system develops at different rates in the sexes, we hypothesized that females and males would respond differently to these perinatal treatments. Pregnant dams were given saccharin (control) or saccharin + 25 mM choline in their drinking water from embryonic day 10 to birth, spanning the critical period for BF neurogenesis. On PN1, some pups received electrolytic lesions to the BF. As adults, the offspring performed fear conditioning, and dark cycle locomotor activity was assessed. Both male and female mice with PN1 BF lesions were hyperactive relative to nonlesion controls; choline did not alter motor activity in either sex. In contextual conditioning (CX) in males, there was a tendency for the lesion to impair performance and choline to improve performance. In females, there was no lesion effect, however, choline tended to improve CX. In cued conditioning (CD) in males, the lesion had no effect, however, choline significantly impaired performance. In females, the lesion tended to impair CD performance, however, choline had no effect. These data suggest that the sexes respond differently to choline supplementation, and males are more sensitive to this manipulation than females.

64. EFFECTS OF NEONATAL BILATERAL AMYGDALA LESIONS ON GROUP SOCIAL DYNAMICS IN ADULT RATS. Kelly, S. J.; Gerritts, M. A. F. M., Wolterink-Donselaar, I. G.; van Ree, J. M. Department of Psychology, University of South Carolina, Columbia, SC USA and Department of Pharmacology and Anatomy,

Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands. Early neonatal lesions of the amygdala result in a cascade of neural changes beyond the amygdala and results in behavioral deficits including decreased social behavior and changes in open field behavior. These effects are different from those of amygdala lesions in adults and may model neurodevelopmental disorders such as autism or schizophrenia. In the current study, male rat pups were anesthetized and received stereotaxic bilateral ibotenic acid lesions of the amygdala on postnatal day 7. Histology confirmed that the lesions always included the region of the basolateral amygdala and did not encroach on surrounding areas. Another set of rat pups received sham lesions on postnatal day 7. After weaning, rats were housed in pairs that were the same sex and lesion group. In addition to the experimental animals, nontreated control male rats of the same age were also included in the study; these rats were habituated in groups of four for 5 min per day for four days in an open field. At 60 days of age, the experimental rats were each tested with four nontreated control rats in the open field for 5 min for four consecutive days. Then the experimental rats were housed in isolation and tested after 1 and 6 days of isolation. The groups are referred to as either lesioned or sham groups depending on the treatment of the experimental animal. The social interactions of the rats were tracked automatically using the Ethovision program (Noldus). Both experimental and control animals in the lesioned groups spent less time in the middle portion of the open field compared to those animals in the sham groups. Experimental and control animals spent less time in proximity in the lesioned groups than in the sham groups. Overall, these results confirm that neonatal lesions of the amygdala do alter social interactions in adult rats and these alterations are reflected in altered group dynamics such that the lesioned rats have less social contact than sham rats.

65. ULTRASONIC VOCALIZATIONS ALTERED DUE TO TESTING TIME AND A CHANGE IN DIETARY PHYTOESTROGENS INTAKE DURING GESTATION AND NURSING. Kunkel, A.J.; Becker, L.A. Department of Psychology, University of Evansville, Evansville, IN 47722-0002 USA. Phytoestrogens are plant-derived estrogens primarily found in soy that are very similar in structure to human steroidal estrogen (Messina, 1994). Recently, perinatal exposure to isoflavones such as genistein has been shown to alter immune function (Klein, Wisniewski, Mason, Glass & Gearhart, 2002) and testosterone levels in adult male rats (Klein, et al., 2002; Johnson, Williams, & Becker, 2001). Prior evidence from our laboratory suggested that phytoestrogens might alter the response to separation from the nest during the prenatal period (Johnson, Williams, & Becker, 2001). In this study, we took 30 minute records of the ultrasonic vocalizations of offspring from female rats that received either a free-feeding diet of normal rat chow rat chow free of soy protein or the rat chow free of soy and given a genistein and diosgenin supplement. The diets were started at the second week of pregnancy and were maintained until weaning at Day 21 (DOB = day 1). In order to examine the separation response we recorded USV for animals during either the light or dark phase of the light/dark cycle. USVs were recorded on postnatal days 5, 10 and 15 showed a response according to the day of test, test time, and phytoestrogen treatment. We are currently correlating these responses with corticosterone levels. These preliminary results suggest that there may be subtle but significant effects on emotional responding in offspring that were exposed to plant estrogens during early development that is dependent upon the time of day in which the animal is separated from the nest.

66. CENTRAL EFFECTS OF EARLY EXPERIENCE IN THE BORDERLINE HYPERTENSIVE RAT. Kobsa, S.; Sanders, B.J.; Anticevic, A., and Dale, D. Department of Psychology, Drake University, Des Moines IA 50311 The interaction of experience and biology can have a profound influence on the way an organism reacts to novel or stressful situations. Moreover, those experiences which occur early in life can have an enduring impact on a range of future biobehavioral responses. One such early manipulation is cross-fostering, in which pups are raised either by their natural mothers or dams of a different strain. Our lab has used the borderline hypertensive rat, which is a cross between the normotensive Wistar-Kyoto (WKY) and spontaneously hypertensive rat (SHR) to examine these relationships. We have shown previously that BHR pups raised by WKY dams exhibit significantly lower blood pressure in response to acute stress compared to BHR raised by their natural SHR mothers. In this study, we used the cross-fostering paradigm to extend these findings and examine the effect of this early manipulation on adult behavioral, cardiovascular and neurobiological parameters during acute stress. Adult BHR cross-fostered to WKY dams exhibited lower blood pressure and engaged in more open field exploratory activity compared to controls. A different group of subjects were subjected to 30 min of restraint stress for determination of c-Fos protein activity, an indicator of neuronal activation, using immunohistochemistry. These data indicate significantly lower levels of Fos activity in the paraventricular nucleus of the hypothalamus, a major integrative areas for the stress response, in BHR raised by WKY dams. Finally, we are using microdialysis to explore stress-induced neurochemical responses in these subjects. Taken together, the current data suggest that early experience, in the form of cross-fostering, can reduce the stress reactivity of the BHR.

67. ANABOLIC STEROIDS INDUCE SEX-SPECIFIC INHIBITION OF SOCIAL BEHAVIORS IN C57BL/6. J Barreto, J Barreto-Estrada, Y Fortis, G Corretjer, JC Jorge* Department of Anatomy, Medical Sciences Campus, University of Puerto Rico 00936. It has been shown that rodent social behaviors can be used as a good experimental model to study human psychiatric disorders. We decided to study spontaneous social behaviors in C57Bl/6

according to sex. The social interaction test was used to evaluate aggression, defensive status and co specific interactions. The parameters measured included: general sniffing, anal sniffing, following, posture attacks, bites, tail rattling, chasing, mounting, body contact, escape, grooming and submissive position. Behavioral observations were conducted during the dark phase of the light-dark cycle. C57Bl/6 mice from same age and sex were randomly paired; a control and an experimental mouse were placed in a Plexiglas arena (30.5 cm x 30.5cm x 19.4 cm) for a 5 min session. The arena was illuminated by red light (15 watts). All experimental sessions were recorded with an infrared digital video camera. The first goal was to determine if various social encounter measures were sexually dimorphic. A second goal was to determine if chronic exposure to anabolic androgenic steroids (AAS) induced a change of social behaviors in mice. Chronic exposure to AAS was achieved using an osmotic pump (Azlet Co.) filled with 17 β -methyltestosterone (7.5 mg/kg) during 14 days. The following social behaviors were more frequent in females vs. males: anal sniffing (p \leq 0.004), following (p \leq 0.01), posture attacks (p \leq 0.04), tail rattling (p \leq 0.03), body contact (p \leq 0.008) and escape (p \leq 0.02). In addition we found that chronic exposure to AAS induced an increase in anal sniffing (p \leq 0.02), chasing (p \leq 0.05), and mounting (p \leq 0.02) in females but not males. We conclude that social behaviors in C57Bl/6 mice are sexually dimorphic. Furthermore, chronic exposure to AAS inhibits male social interactions. Support for this study was provided by the BRIN-PR Program (RR16470 from the National Center for Research Resources, NCRR-NIH).

68. EFFECT OF LESIONS TO THE DORSAL PREMAMMILLARY NUCLEUS ON DEFENSIVE BEHAVIORS. Markham, C.M.; Li, C.; Cuyano, C.; Blanchard, R.J.; Takahashi, L.K.; Blanchard, D.C. Dept of Psychology and the Pacific Biomedical Research Center, University of Hawaii, Honolulu, HI 96822 USA. Recent studies have suggested that the Dorsal Premammillary Nucleus (PMd) may play a key role in the modulation of defensive responding to non-painful, unconditioned threat stimuli. The PMd forms part of a distinct circuit of structures, which includes the bed nucleus of the stria terminalis, midbrain periaqueductal gray, lateral septum and precommissural nucleus, that are activated during exposure to these threat stimuli. For example, rats exposed to both predator and predator odors (Canteras, et al., 1997, Dielenberg, et al., 2001) exhibited increased expression of Fos immunoreactivity in the PMd. Furthermore, lesions to the PMd have been shown to virtually eliminate freezing behavior in rats during exposure to a cat (Canteras, et al., 1997). These studies however, did not assess the full spectrum of defensive behaviors following lesions to the PMd. The present study therefore examined the effect of electrolytic lesions to the PMd on patterns of defense elicited by the elevated plus maze (EPM), footshock as well as responses to both predator and predator odor.

69. HYPOCRETIN2-SAPORIN (HCRT2-SAP) LESIONS OF THE LATERAL HYPOTHALAMUS DOES NOT AFFECT THE ENTRAINED OR FREE-RUNNING RHYTHM OF CORE BODY TEMPERATURE. Dmitry Gerashchenko, Blanco-Centurion, C, and Shiromani PJ. West Roxbury VA Medical Center-Harvard Med School, 1400 VFW Parkway, West Roxbury, MA, 02132 Hypocretin (HCRT) containing neurons are present only in the lateral hypothalamus (LH) from where they project heavily to the major arousal centers. HCRT neurons are lost in the sleep disorder narcolepsy, an illness characterized by an increased tendency to fall asleep during the normal active period. Because of these findings it is hypothesized that HCRT neurons are responsible for “waking-up” the brain. To test this hypothesis we monitored the rhythm of core body temperature during entrained and free-run (lights-off) conditions in rats after lesions of the HCRT neurons. 23 male Long-Evans rats were implanted with sleep recording electrodes and a temperature transmitter. Two concentrations (90 ng/0.5 μ l vs 490 ng/0.5 μ l) of the neurotoxin hypocretin2-saporin (HCRT2-SAP) or unconjugated saporin were given to the LH to lesion HCRT neurons. Control rats received saline (n=5). After surgery, sleep and temperature were continuously recorded for 21d in entrained conditions followed by 21d in continuous darkness. The two concentrations of the HCRT2-SAP lesioned equal number of HCRT neurons (88%, 91%). However, HCRT2-SAP lesions did not disrupt the entrained rhythm of core temperature by either advancing or delaying the phase position of the temperature rhythm. In the saline rats, the free-run period of temperature rhythm (τ) was 24.16 (\pm 0.07) and this was not significantly different in the HCRT2-SAP or SAP rats. This indicates that the lesions of the LH and HCRT neurons did not affect the phase or period of the endogenous rhythm of core temperature. This rules out the HCRT neurons as being responsible for receiving a signal from the SCN and “waking-up” the rest of the brain. Supported by DVA Med Research, NS30140, AG15853 & AG09975, MH55772.

70. ACTIONS OF CART ON NEURONAL ACTIVITY OF THE VENTRAL TEGMENTAL AREA IN RATS. Sasaki, K.¹; Otsubo, Y.¹; Ishibashi, M.¹; Oomura, Y.² ¹Div. of Bio-Information Eng., Fac. of Eng., Toyama Univ., Toyama, 930-8555 Japan; ²Dept. of Physiol., Fac. of Med., Kyushu Univ., Fukuoka, 812-8582 Japan. Cocaine- and amphetamine-regulated transcript (CART) is a newly identified neuropeptide that is up-regulated by psychoactive drugs, cocaine or amphetamine. Recent studies show that microinjection of CART fragment (CART 55-102) into the ventral tegmental area (VTA) increases locomotor activity and induces place preference. In the present study, hence, we examined effects of CART on neuronal activity of the VTA in rats using brain slice preparations under normal or low Ca²⁺ and high Mg²⁺ Ringer solution. The neurons recorded were identified as dopamine neurons through electrophysiological criteria. Application of 10⁻⁹M, 10⁻⁸M and 10⁻⁷M CART inhibited 0%, 17% and 32% of VTA

neurons recorded, respectively. There were no neurons excited by CART. The inhibition induced by CART under normal Ringer solution was also observed under low Ca^{2+} and high Mg^{2+} Ringer solution. Co-administration of D_2 receptor antagonist, sulpiride, blocked the inhibitory effects of CART to the VTA neurons. These results suggest that CART has inhibitory effects on VTA neurons like cocaine and amphetamine and that CART may exert a psychostimulant-like effect via this inhibitory effects on VTA neurons.

71. FUNCTIONAL INTERACTIONS BETWEEN DOPAMINE ET GLUTAMATE NEUROTRANSMISSIONS. David, H.N.; Abraini, J.H. UMR CNRS 6551, CYCERON, Université de Caen, Caen, France. The basal ganglia provide a major neural system that integrate cortical information, process and re-direct it to the cortex. The striatum, the basal ganglia major input structure, receives glutamate projections from the whole cortex and from the thalamus and dopamine projections from the substantia nigra pars compacta and the ventral tegmental area. Functional interactions in the regulation of the activity of striatal neurons and the expression of related behaviour between these two neurotransmissions have often been described. Numerous studies reported that dopamine and glutamate in the nucleus accumbens, the ventral part of the striatum, would also be involved in the expression of the behaviourally-activating properties of mental disorders. The aim of our work was to characterize the functional interactions in the nucleus accumbens between dopamine and glutamate in normal behaviours in order to understand the neurochemical alterations underlying the behaviourally-activating properties of mental disorders. We have characterized the regulation of the locomotor responses induced by the activation of the dopaminergic receptors and by the acute infusion of D-amphetamine by group I, II and III metabotropic glutamate and NMDA and non-NMDA ionotropic glutamate receptors. Our results show complex functional interactions that depend of the type of receptors involved. Given our results, we suggest (i) the current model of basal ganglia organisation should to be complexified in order to take into account the limbic or sensory-motor origin of the glutamate projections to the striatum; (ii) the locomotor-activating properties of amphetamine should no longer be considered as the consequence of an action on dopamine neurotransmission but of the consequence of complex mechanisms in which glutamate plays a crucial role.

72. MEASUREMENT OF DRUG INDUCED CHANGES IN THE ELECTRICAL ACTIVITY OF ACUTE BRAIN SLICES FROM BLUEGILL SUNFISH AS A SURROGATE FOR FISH BEHAVIOR Rossi III, J.; McInturf, S.; McDougle, F.; Bekkedal, M.; Ritchie, G. Neurobehavioral Effects Laboratory, NHRC/TD, WPAFB, OH 45433-7903 USA. Currently, the U.S. Army employs a system that monitors changes in the behavior of bluegill sunfish as a means of detecting alterations in water quality. The present study used a planar microelectrode array system (Panasonic MED64) to develop a system to act as a surrogate for fish behavior. Initially, we determined that fish brain would provide viable slices for use with the MED64 System. Thirty two 500 μM slices obtained from the optic tectum of bluegill sunfish were attached to 64-electrode microelectrode arrays. Electrode sites were successively stimulated, and presence of evoked response activity was assessed at each of the 63 remaining electrode sites. Test electrode pairs were then chosen for each brain slice. The biological nature of the responses was demonstrated by elimination of the responses with the sodium channel blocker tetrodotoxin. Slices were then treated with ethanol, and dose dependent reductions in evoked response amplitude were observed. We then tested the ability of the slice response to model the behavioral responses of the fish. Previously, we collected behavioral data following exposure of the fish to trimethylolpropane phosphate (TMPP), a GABA-A chloride channel suppressor. Slices treated with TMPP exhibited dose related increases in amplitude of the evoked responses. These effects were consistent with those delivered to the intact fish. Slices treated with the GABA-B agonist baclofen were also found to predict the behavioral responses. Phaclofen, a GABA-B antagonist, was found to produce the opposite effect.

73. TARGETED GENETIC REDUCTION OF GABAA RECEPTOR $\alpha 2$ SUBUNITS REDUCES ETHANOL-INDUCED SPATIAL MEMORY IMPAIRMENTS IN MICE. R.B. Berry¹, D. Chandra², G.E. Homanics² & D.B. Matthews¹. 1. Department of Psychology, University of Memphis, Memphis TN 38152; 2 Dept. Anesthesiology, University of Pittsburgh, Pittsburgh, PA 15261 The selective impairment of spatial memory following acute ethanol administration has been shown in multiple tasks using both mice and rats. However, the underlying molecular mechanism producing ethanol induced spatial memory impairments has yet to be investigated. Ethanol interacts with several neurotransmitter systems including GABAA receptors. Although controversial, it has been suggested that the GABAA receptor $\alpha 2$ subunit modulates ethanol responses. To further test this hypothesis, male wild type (C) and GABAA receptor $\alpha 2$ heterozygous knockout (KO) mice were trained on a spatial task in the Morris Water Maze for 15 days using a balanced Latin square design. Control and knockout animals learned at approximately the same rate (Two-Way ANOVA, $\text{df}(14,60)$ $F = 0.32$, $p > 0.05$). Following training, an ethanol test was administered, where each mouse was given an injection of one of four randomly assigned doses: saline (1.75 g/kg), low ethanol (1.25 g/kg), medium ethanol (1.75 g/kg), or high ethanol (2.25 g/kg). Thirty minutes post-injection, the mice were tested in the spatial task. Preliminary results indicate that acute ethanol administration impairs spatial memory, as measured by path length, in control animals but does not impair spatial memory in KO animals. Furthermore, this impairment was selective to spatial memory in that acute ethanol administration did not disrupt swim speed or produce differential blood ethanol levels between control or KO animals. While preliminary, these results suggest that the

GABAA receptor $\alpha 2$ subunit might modulate ethanol-induced spatial memory impairments in mice. Supported by NIH grants AA10422 and DE14184.

74. CHRONIC INTERMITTENT ETHANOL EXPOSURE IN ADOLESCENT RATS PRODUCES TOLERANCE TO ETHANOL-INDUCED SPATIAL MEMORY DEFICITS: AN INVESTIGATION OF POSSIBLE MOLECULAR MECHANISMS. J. M. Silvers¹, S.B. Goodwin², T.R. Sutter², A.L. Morrow³, and D.B. Matthews¹ ¹Department of Psychology, University of Memphis, Memphis, TN 38152 ² Department of Microbiology and Molecular Cell Sciences, University of Memphis, ³ Bowles Center for Alcohol Studies, University of North Carolina-Chapel Hill, School of Medicine, Chapel Hill, NC 27599. Adolescence is a period of unique sensitivity to the effects of chronic intermittent ethanol (CIE) exposure. In previous studies, we have demonstrated profound metabolic tolerance and tolerance to ethanol-induced loss of righting reflex in response to CIE exposure. Both of these forms of tolerance were long lasting and evident at 12 days following cessation of CIE exposure. We have also shown that CIE exposure during adolescence produces tolerance to ethanol-induced spatial memory deficits, which is not seen after 12 days. In the current set of studies, adolescent rats were administered 5.0 g/kg (i.p.; 20% conc.; w/v) ethanol or equivalent saline at 48-hour intervals from postnatal day (P)30 to P50. Following pretreatment, all animals were tested on a spatial memory task in the Morris water maze, or were sacrificed for determination of allopregnanolone levels following ethanol or saline challenge. In saline pretreated animals, ethanol challenge produced spatial memory deficits in a dose dependent manner while animals pretreated with ethanol showed no spatial memory deficits in response to an ethanol challenge. Ethanol pretreatment produced a significant increase in allopregnanolone levels in hippocampus and cortex that was significantly reduced by ethanol pretreatment. When testing was repeated 12 days later, both pretreatment groups showed spatial memory impairments, and both pretreatment groups displayed increased allopregnanolone levels in response to an ethanol challenge. Currently, studies are underway that seek to investigate underlying mechanisms in these forms of tolerance in adolescent rats. Specifically, novel animals underwent the above pretreatment. Following pretreatment, hippocampus and liver were removed, and RNA was isolated. RNA will be run on Affymetrix GeneChip arrays in order to detect differences in gene expression related to CIE exposure and to investigate the possible molecular mechanisms that underlie adaptations and tolerance brought on by CIE exposure.

75. ALLOPREGNANOLONE NEUROGENESIS ALTERS ETHANOL'S EFFECT IN THE HIPPOCAMPUS. S. Tokunaga¹, A.L. Morrow², and D.B. Matthews¹ ¹ Department of Psychology, University of Memphis, Memphis TN 38152 ² Bowles Center for Alcohol Studies, University of North Carolina-Chapel Hill, School of Medicine, Chapel Hill NC 27599. Acute ethanol administration impairs performance on many hippocampal-dependent cognitive tasks and concomitantly alters hippocampal neurophysiology. Ethanol administration also elevates circulating levels of several neuroactive steroids including 3 α -hydroxy-5 α -pregnan-20-one (allopregnanolone), and blockade of de novo allopregnanolone biosynthesis alters many effects of ethanol. Acute ethanol administration has been found to inhibit spontaneous hippocampal pyramidal cell neural activity. In order to study if allopregnanolone modulates ethanol's inhibitory effect on hippocampal pyramidal neurons, we investigated the effect of finasteride, a 5 α -reductase inhibitor, on ethanol-induced inhibition. We also investigated the effect of finasteride preadministration on ethanol-induced impairments in watermaze performance. Adult male Long-Evans hooded rats were anesthetized with urethane and a hole was drilled in the skull overlying the hippocampus. A single-barrel glass micropipette was lowered into the hippocampus until a single pyramidal neuron was well isolated. In finasteride condition, rats were administered finasteride (50 mg/kg) subcutaneously at 4 and 1.5 hours before the surgery. Following a 5-minute baseline recording, 1.5g/kg ethanol was administered and the neuron was recorded for an additional 60 minutes. In the watermaze study, rats were trained a spatial task in watermaze, then were tested with ethanol administration (saline control, 1 g/kg, 1.5 g/kg or 2 g/kg), following either preadministration of vehicle or finasteride (50 mg/kg). Both studies found that preadministration of finasteride prevented the effect of ethanol. The findings from these studies indicate that allopregnanolone plays an important role in producing ethanol-induced changes in hippocampal function. AA10564 (ALM).

76. DOSES OF ESTRADIOL VALERATE (EV) AND FEMALE RATS' APPETITE FOR ALCOHOL. Reid, L.D.; Ledesma de la Teja, S.; Sanchez, M.A.; Reid, M.L.; Diaz-Trujillo A.; Prado-Alcala, R.A. Instituto de Neurobiologia, UNAM and U. Queretaro, Queretaro, Mexico. At the last two meetings, we presented data relevant to our studies of female rats and appetite for alcohol. Beginning some days after an injection of EV, females have enhanced appetites for alcoholic beverages that are sustained for many as 100 days. This year, we present further dose-response data with measures of estradiol levels. We initially anticipated that a single injection of EV provided a steady level of estradiol across days. That is not the case; rather, there is a large peak of estradiol shortly after an injection that diminishes slowly across days. At 27 days, after a single injection of 10 mg of EV/kg, there is still a higher level of circulating estradiol among EV-treated females compared to placebo-treated: EV-mean = 131.7 pg of estradiol/ml of plasma (SD = 87.7); placebo-mean = 53.2 pg/ml (SD = 20.3)(p = .001). At 67 days after an injection of similar doses, levels of estradiol of EV- and placebo-treated females were similar. Notably, intakes of alcoholic beverages were enhanced at both the 27th and 67th days after EV injection among rats treated similarly to those for

which we have measures of estradiol. From these data, we infer that the events critical to the enhanced appetite for alcoholic beverage are not a product of complete withdrawal from higher levels of estradiol as we originally thought.

77. POSTCESSATION CHANGES IN FOOD SELECTION IN POSTMENOPAUSAL WOMEN. Geiselman, P.J.; Martin, P.D.; Copeland, A.L.; Ryan, D.H.; Bordelon, J.R.; and Neal, J.L. 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, and middle-aged women gain more weight postcessation than do younger women. Also, 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 contributing factor in postcessation weight gain, the issue of effects of smoking and 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. Postmenopausal smokers were tested in our macronutrient self-selection paradigm (MSSP) while still smoking. They were then enrolled in a two-week smoking cessation program, which was immediately followed by a 20-month follow-up intervention aimed at dietary control and weight management. Subjects used a nicotine patch for the first eight weeks postcessation. At one month postcessation, MSSP tests were repeated. Preliminary results suggest that postmenopausal women who quit smoking tend to increase their intake of high fat/high sugar foods. 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 postmenopausal women following smoking cessation. Supported by NIH grant AG18239.

78. LONG TERM EFFECTS OF TRANSDERMAL NICOTINE ON MOOD AND SLEEP. Haro, R.; Drucker-Colín, R. Clínica de Trastornos de Sueño, Facultad de Medicina and Departamento de Neurociencias, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México. Acute administration of nicotine has been shown to have beneficial effects on a variety of neurological and psychiatric disorders. Depression is the most prevalent psychiatric disorder and it is usually associated with sleep disturbances. Therefore, the purpose of this study was to determine the long term effects of transdermal nicotine administration on sleep and major depression. Fourteen non-smoking patients with a Hamilton Rating Scale for Depression > 18 served as subjects. Nicotine transdermal patches (17.5 mg) were administered five days weekly for six months, at the 7th month nicotine was administered during three days, and on the 8th month only one day per week. From the 9th to the 24th month, the nicotine patch was substituted by a patch without nicotine. Sleep recordings and evaluation of depressive symptoms was carried out every month for the duration of the study. A group of 35 healthy subjects was used as control. The results showed REM sleep latency changes from 32.6 min. to 78.2 min. at the end of the study; a significant decrease of wakefulness and a permanent increase of slow wave sleep throughout the study, as well as a transient decrease of REM sleep duration upon nicotine withdrawal. Hamilton scores were modified from an initial mean score of 29.7 to a final score of 10.8. The results show that mood and sleep alterations observed in depressed patients herein studied improve after chronic administration of transdermal nicotine and that this seems to carry over throughout the nicotine withdrawal period.

79. GENETIC AND BEHAVIORAL DIVERSITY OF MOUSE STRAINS AND SUBSTRAINS. Bothe, G. W. M., Vedder, M. J., Geistfeld, J. G., Taconic Biotechnology, Rensselaer, NY 12144, USA. Five strains and substrains of mice commonly used in transgenics were compared with regard to genetic background and behavior. Those strains were: C57BL/6J, C57BL/6NTac, 129P3/J (formerly named 129/J), 129S6/SvEvTac (formerly named 129/SvEvTac), FVB/NTac. 342 microsatellite markers were compared, and performance in the behavior tests, RotoRod, Habituation to an Open Field, and Contextual and Cued Fear Conditioning, was determined. Results will form a basis for the planning and evaluation of transgenic and knockout models of neurodegenerative diseases. The five inbred mouse strains were found to belong to three groups genetically. C57BL/6J and C57BL/6NTac were closest to each other. Only 12 polymorphisms were found, and marker sizes varied by only two or four base pairs. This is consistent with the two strains being true substrains that have diverged by point mutation or DNA polymerase slippage only, and with the genetic divergence being very small. Given the data on the genetic background, one might predict that the two B6 substrains should be very similar behaviorally. To test this hypothesis, behavior testing was performed. Behavioral differences between the five strains generally followed the genetic differences. Contrary to literature reports on other 129 group strains, 129S6/SvEvTac often performed similar to B6 strains. On the Rotorod between day 1 and day 3, latency to fall increased 110% in female 129S6, 100% in female C57BL/6NTac, but only 25% in female FVB/NTac. FVB/NTac was the only strain that did not show habituation of horizontal activity on the 4th daily trial in the Open Field, and low responses to context and cue after Fear Conditioning.

80. TRANSGENIC MICE EXPRESSING A TRUNCATION MUTANT OF CBP EXHIBIT SPATIAL MEMORY DEFICITS. Wood, M.A.; Lombardi, T.L.; Park, A.; and Abel, T. Department of Biology, University of

Pennsylvania. Studies in *Aplysia*, *Drosophila* and mice have shown that the transcription factor cAMP response element binding protein (CREB) is involved in the formation of long-term memory. Following phosphorylation by protein kinase A (PKA), CREB interacts with the CREB-binding protein (CBP) to induce expression of cAMP-dependent genes. CBP is a large nuclear protein that acts both as a histone acetyltransferase and a transcriptional coactivator. Although the role of CREB in learning and memory has been extensively studied, the function of CBP in memory remains largely unknown. Deletions, translocations, or point mutations in the CBP gene have been associated with Rubinstein-Taybi Syndrome (RTS), a human developmental disorder characterized by retarded growth and reduced mental function. Recently, in a mouse model of RTS, CBP was shown to be necessary for normal development and long-term memory. However, developmental defects could not be separated from memory deficits and thus the role that CBP plays in memory remains unanswered. To more clearly examine a possible function for CBP in memory, transgenic mice were generated in which the CaMKII α promoter drives the expression of a CBP truncation mutant in forebrain neurons. The truncated CBP protein is predicted to interrupt CREB-mediated transcription. We have analyzed three independent lines with different levels of transgene expression. The highest expressing line demonstrates significant memory impairments as observed in the spatial version of the Morris water maze. These results suggest that CBP may play a role in learning and memory, perhaps by acting as a coactivator for transcription factors such as CREB.

81. SEX DIFFERENCES IN PPI OF MICE LACKING NR3A SUBUNITS S.A. Brody¹, N. Nakanishi², S.A. Lipton², M.A. Geyer¹ ¹UCSD and ²The Burnham Institute, San Diego, CA. The NMDA subtype of glutamate receptor is composed of multiple subunits (including NR1, NR2A-D, and NR3A-B), but with unknown stoichiometry. Peak expression of the NR3A subunit occurs approximately 2-3 weeks postnatally, although low levels persist into adulthood. Among other properties, the presence of the NR3A subunit reduces NMDA current, and in combination with NR1 subunits forms a glycine-sensitive channel. The NR3A subunit is located primarily in the amygdala, hippocampus, striatum, and cortex. All of these regions are involved in the modulation of prepulse inhibition of the startle response (PPI), an operational measure of sensorimotor gating. NMDA receptors have been shown to be important in the modulation of PPI. To examine the role of the NR3A subunit, NR3A knockout (KO) mice were generated using 129/SvJ-derived ES cells and C57BL/6-derived blastocysts. The chimeras were crossed with BlackSwiss and all mice used in these studies were the offspring of heterozygous matings. NR3A KO mice and their littermate counterparts were tested repeatedly in a PPI paradigm as they developed from weaning (3-4 weeks) through adulthood (14 weeks). The KO mice appeared healthy, and exhibited comparable startle magnitude to their wildtype (WT) and heterozygous (HET) littermates. Male NR3A KO mice exhibited an increase in PPI 3-4 weeks postnatally, while female NR3A KO mice did not differ from their WT or HET counterparts at any of the ages tested. This sex-specific increase in PPI is consistent with the antagonistic role of the NR3A subunit in the NMDA receptor as well as the observation that estrogen modulates NMDA receptor function.

82. ALPHA4-CONTAINING NEURONAL NICOTINIC RECEPTORS MODULATE APPETITIVE LEARNING. Wehner, J.M.1; Balogh, S.A.1; Bowers, B.J.1; Logue, S.F.1; Ernise, J.1; Labarca, C.2; Lester, H.A.2. ¹Institute for Behavioral Genetics, University of Colorado, Boulder, CO; ²California Institute of Technology, Pasadena, CA. The present study characterized the role of alpha4-containing nAChRs in learning and memory using a four-stage appetitive signaled-nosepoke task in 13 inbred mouse strains and in a gain of function alpha-4 nicotinic receptor mutant. In inbred mouse strains, a naturally occurring polymorphism in the mouse alpha4 neuronal nicotinic receptor subunit gene encodes either an alanine or threonine (A/T) at position 529. This A/T polymorphism is associated with differential receptor function and behavioral sensitivity to nicotine and ethanol in both inbred and recombinant inbred mouse strains. The first three phases of the nosepoke task consisted of training to associate an auditory cue with reinforcer availability. The last phase required that each mouse nosepoke only when the cue was presented. Inbred mouse strains with the 529alanine form of the polymorphism required a significantly greater number of days to learn to associate the auditory cue with the reward than those containing the 529threonine residue. Alpha4^{+/m} mice with a leucine to serine mutation near the gate of the gate in the channel pore are hypersensitive to nicotine and have several behavioral alterations. Alpha4^{+/m} mice showed enhanced associative learning in the signaled nosepoke task, relative to their wild type littermates. These data suggest that nAChRs that contain the Alpha4 subunit modulate appetitively-motivated associative learning. (supported by CTRP 2R-033 to J.M.W. and NS-11756 and TRDRP to H.A.L.)

83. OBJECT EXPLORATION IN DARPP-32 KNOCKOUT MICE. Heyser, C.J.; Owens, C.H.; Pelletier, M.N.; Werner, J.L.; Fienberg, A.A.; & Greengard, P. Franklin & Marshall College, Dept. of Psychology, Lancaster, PA 17604; The Rockefeller Institute, Lab. of Molecular and Cellular Neuroscience, New York, NY, 10021. Dopamine- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) is critically involved in mediating the biological effects of dopamine. Given the potentially significant role of dopamine in learning and memory systems, the present study was conducted to examine adult male and female DARPP-32 knockout mice and their wild-type controls in an object exploration task. The advantages of this task are that there is no explicit need for food or water restriction and several behavioral endpoints can be obtained including general activity, along with measures of learning (e.g.

recognition memory). Testing was conducted in a large circular arena and consisted of five 6-min trials (Trial 1-no objects, Trial 2-the open field contained four different objects, Trial 3 and 4-the four objects from Trial 2 remained in the open field, Trial 5-one of the objects was replaced with a novel object). Wild-type and knockout mice exhibited comparable behavior during the first 4 trials. As expected, wild-type mice increased exploration of the novel object in Trial 5, demonstrating recognition memory. In contrast, knockout mice did not show preferential exploration of the novel object, with these mice exhibiting an increase in exploration of all objects during Trial 5. These results do not appear to be due to alterations in activity or propensity to explore objects per se, since there were no differences in these measure during the first 4 trials. Therefore, these results suggest that DARPP-32 mice have impaired recognition memory and/or reactivity to or preference for novelty.

84. BEHAVIORAL ANALYSIS OF MICE LACKING EXPRESSION OF NEURONAL OR ASTORCYTIC NFkappa-B. A.J. Bramwell¹, E.J. Green¹, and J.R. Bethea² ¹Psychology Dept, University of Miami ²Miami Project to Cure Paralysis, University of Miami School of Medicine, Miami, Fl. USA. Nuclear factor kappa-B (NFk-B) is an important transcription factor that is shown to play a significant role in synaptic plasticity possibly via a pathway that prevents neuronal apoptosis. NF- kB may also play a role in learning and memory because it is activated by synaptic activity. In its inactive form, NFk-B is localized in the cytoplasm attached to Ikb-alpha, its endogenous inhibitor. To more clearly delineate the role of NFk-B in the CNS, we created two independent lines of transgenic mice over-expressing a dominant negative Ikb-alpha gene in neurons or astrocytes. Evaluation of the animals' general health showed no overt abnormalities. Cognitive and sensori-motor functions were extensively quantitated using behavioral paradigms in the Barnes circular maze and Morris water maze, open field test, and the light-dark anxiety test. Evaluation of the animals' anxiety level indicated normal response on the light-dark test. On the open field task, neither males nor female transgenic animals were different from the wild type. Analyses of the Barnes' circular maze data indicated that females (GFAP and synapsin) but not male mice exhibited significantly longer latencies on the cued version of the task when compared to wild types. In addition, during a probe trial following the hidden goal task, female synapsin animals spent significantly less time in the region of the maze that contained the goal box. Additional cognitive assessment of the female transgenics in the Morris water maze has thus far revealed no significant differences between the two transgenic groups or wild type females. Further behavioral analysis of these transgenic animals using a battery of well-establish behavioral tasks will contribute to the elucidation of these gender-specific deficits and an understanding of the extent to which NFk-B participates in learning and memory per se or other behaviors that may affect performance on these tasks.

85. BDNF CONDITIONAL MUTANTS EXHIBIT ALTERATIONS IN SEROTONIN (5-HT) NEUROTRANSMISSION. Rios, M.¹, Liu, R.², Lambe, E.², Jaenisch, R.³, and Aghajanian, G.² ¹Department of Neuroscience, Tufts University School of Medicine, Boston, MA; ²Department of Psychiatry, Yale University, New Haven, CT; ³Whitehead Institute, Cambridge, MA. Brain derived neurotrophic factor (BDNF) is a member of the family of neurotrophins and the ligand for the TrkB receptor. Recently, we generated a line of BDNF conditional mutant mice using the cre recombinase-loxP system. These mutants have a postnatal depletion of BDNF in the central nervous system that does not compromise viability but leads to hyperphagia, hyperaggression, and an increase in anxiety-related behavior. Previous studies showed that BDNF increases turnover of serotonin and induces sprouting and regeneration of serotonergic neurons. In addition, infusion of BDNF near the raphe nucleus, a site containing serotonergic cell bodies, has an anti-stress effect. Here, we performed electrophysiological recordings in brain slices containing prefrontal cortex or dorsal raphe nucleus. Abnormal responses to 5-HT were observed both at the pre and post synaptic sites in the mutants. In BDNF mutants, stimulation of 5-HT_{2A} receptors in pyramidal neurons of the prefrontal cortex resulted in a markedly attenuated response, whereas 5-HT_{1A} autoreceptors in 5-HT neurons in dorsal raphe nucleus were hypersensitive to 5-HT. In addition, accumulation of the second messengers IP3 and cAMP, normally induced or inhibited by activation of the 5-HT_{2A} and 5-HT_{1A} receptors, respectively, was affected in the mutants. These data indicate two mechanisms through which 5-HT neurotransmission is altered in BDNF conditional mutants and which could contribute to the changes in observed behavior. Thus, BDNF may have a postnatal maintenance function in the 5-HT system, which is involved in the regulation of affective behaviors.

86. OBSERVATIONS OF UNUSUAL BEHAVIOR IN CALIFORNIA MICE, *PEROMYSCUS CALIFORNICUS*. Lee, A.W.; Brown, R.E. Department of Psychology & Neuroscience. Dalhousie University, Halifax, NS B3H 4J1 Canada. We have been studying parental behavior in the monogamous California mice (*Peromyscus californicus*), and over the past several years, have also conducted a variety of experiments using California mice as subjects. While doing so, we have observed a number of unusual observations including the following: 1) We have observed mice having seizures during regular cage changes. 2) California mice show a remarkably high level of activity in the open field compared to normal laboratory mice. 3) In the elevated plus maze, 63% of mice did not complete the test because they jumped off the maze, had seizures, or both. Of those that did complete the test, many did not show a preference for the closed arms, showed a high level of activity, and climbed up the walls of the closed arms and walked on the upper ledges of the closed arms. 4) We have found it difficult to perform simple surgeries, as it is

challenging to anesthetize mice using somnitol or ketamine/zylazine, ip or sc. 5) We have attempted in two separate experiments to induce lordosis behavior by ovariectomizing females and injecting them with estradiol benzoate and progesterone, but failed. 6) In a study investigating the distribution of c-fos expression after an interaction with pups, we found no difference between pup-experienced and control mice in the medial preoptic area, an area known to be critical for maternal behavior in rodents. We will discuss these behaviors in comparison with behaviors of normal laboratory mouse strains. Our findings indicate that many laboratory procedures developed for the domestic *Mus* may not be suitable for *P. californicus* and caution should be used in interpreting the results of such tests with this species.

87. NONLINEAR BEHAVIOR DYNAMICS AS A DEPENDENT VARIABLE IN BEHAVIORAL PHARMACOLOGICAL STUDIES. Li, J.-S.; Huston, J.P. Institute of Physiological Psychology, University of Düsseldorf, 40225 Düsseldorf, Germany. Behavior is a real-time event, and behavioral variables are the products of behavior dynamics of the animals. Consequently, analysis of behavioral changes over time, that is, of time series data sets, is an important tactic for assessing mechanisms that governing behavior. However, the high irregularity of behavioral observations hampers direct analysis of time series. Thus, time series are usually converted into time-invariant entities using statistical methods. In recent years, non-linear dynamical analysis has provided an alternative. A systems' dynamics is presented as trajectories in a phase space, which is constructed by all the independent variables that describe the system. Alternatively, a phase space can be reconstructed from a single time-series data set by application of particular tools. We introduced a new analyzing tool, the Extended Return Map (ERM), to reconstruct a multi-dimensional phase space out of the one-dimensional time series, the inter-response-time, generated from Skinner-box experiments. We found that fixed-interval responding generated distinct patterns in the ERM, which were consequences of switches between behavioral states during the time between two adjacent rewards, as indicated by simulations. These patterns can be regarded as kinds of attractors, which represent the final state of animal behavior under the given conditions. Under certain pharmacological treatments, such as amphetamine, the patterns change, implying a change of mechanisms of behavior dynamics. The study of such changes represents a direct approach toward analyzing mechanisms of behavior under the influence of pharmacological interventions.

Saturday, April 26

8:00-10:00 Symposium 4: Neurobiology of cognition in laboratory animals.

RODENT COGNITION: DEFINING THE ISSUES. Sarter, M. Department of Psychology and Neuroscience Program, The Ohio State University, Columbus, OH 43210 USA. The assessment of cognitive functions in rodents represents a critical experimental variable in many research fields, ranging from the basic cognitive neurosciences to the development of models of cognitive disorders and neurotoxicology. This symposium has been motivated in part by concerns which are emerging from the increasing 'fast and dirty' and assay-like use of behavioral tests for cognitive functions, particularly maze-based tests, and the associated questions about the validity of measures generated by such use of these tests. In animals, as in humans, speculations about, and the experimental determination of, levels of processing (e.g., effortful versus automatic) and categories of information (e.g., allocentric vs. egocentric; based on habits versus on episodic or declarative information) are crucial steps in defining the cognitive function assessed by a behavioral test. The design of tests to assess the recall of 'episodic' or 'declarative' information represents a particular challenge for research using laboratory rodents. For example, it is not clear whether changes in inspection time for a previously encountered place or object indeed reflects a distinct memory about the prior exposure to the place or object, or is based largely on non-cognitive processes. Furthermore, the cognitive variables, specifically the attentional processes and capacities, which mediate changes in cognitive performance in animals have rarely been determined, although the predictive validity of data from animals depend closely on the cognitive nature of effects on performance. This symposium will address these topics by providing a critical analysis of spatial navigation tests (Sutherland), a discussion of approaches designed to assess processing capacity issues in rodents and monkeys (Turchi) and related executive functions in rats (Dalley and McDonald). Given the increasing importance of mouse models in this area, the last talk will focus on special issues concerning the valid testing of cognitive functions in mice (Baron).

COGNITIVE PROCESSES IN SPATIAL LEARNING AND NAVIGATION. Sutherland, R.J.; Hamilton, D.A. Canadian Centre for Behavioural Neuroscience, The University of Lethbridge, Lethbridge, AB T1K 3M4 Canada. Tasks that explicitly tap spatial learning and memory have been of great interest to psychologists and neuroscientists for more than 70 years. Data from measuring rodent navigation have been critical in developing the current understanding of basic learning mechanisms, functions of certain cortical circuits, drug effects, and more recently, gene/behaviour interactions, and certain aspects of human cognitive neuroscience. Despite the fundamental importance, it is surprising that a well-elaborated consensus on basic cognitive processes does not yet exist. Through a critical review of spatial learning and navigation experiments, we will address several conceptual issues. 1. What is

the nature of cues guiding navigation? 2. Can one establish a taxonomy of spatial tasks? 4. Are there distinct laws of spatial learning? 5. What is the nature of the representations that underlie place navigation? 6. How does the hippocampus contribute to spatial processes? 7. What is the nature of the long-term consolidation of spatial information? 8. What are the properties of topographical amnesia in rats? 9. How similar are spatial cognition processes in rats and humans?

NEUROBIOLOGY OF PROCESSING CAPACITY: FROM RATS TO MONKEYS. Turchi, J. Lab of Neuropsychology, NIMH, NIH, Bethesda, MD 20892 USA. Diminution of processing capacity, particularly as evidenced by impairment of divided attention performance, is a prominent characteristic of multiple neuropathologies. For instance, deficits in divided attention correlate strongly with the degree of cholinergic compromise among individuals with dementia of the Alzheimer's type. Assessment of divided attention in humans has typically involved dual-task paradigms; titration of the cognitive demands of each component task allows for finer exposition of the limitations in processing capacity associated with a given clinical disorder. The scant number of rodent models speaks to the challenges inherent in the development of appropriate analogues of these paradigms in the non-verbal context. This presentation will discuss extant rodent and non-human primate models of divided attention. Other mechanisms for the evaluation of processing capacity, including taxation of processing resources by mnemonic load (i.e., list learning, scene learning), will be described as well. Relevant species-specific response biases will be considered as they may pertain to task development and performance interpretation. In addition, ramifications of utilizing multiple-task batteries, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) in non-human primates, will be addressed. Establishment of valid animal models is vital for elucidation of the neurochemical substrates serving these complex cognitive functions. Furthermore, suitably interpretable models will provide useful platforms for the investigation of potential pharmacotherapeutic intervention in progressive neuropathologies affecting cognition.

FRONTO-EXECUTIVE FUNCTIONS IN RODENTS: NEURAL AND NEUROCHEMICAL SUBSTRATES. Cardinal, R.N.; Dalley, J.W.; Passetti F.; Theobald, D.E.; Winstanley, C.A.; Robbins, T.W. Department of Experimental Psychology, Downing St, Cambridge CB2 3EB, UK. The prefrontal cortex (PFC) and associated cortico-striatal circuitry, including interconnections with sensory neocortical and motor systems has been widely implicated in the control and execution of goal-directed behaviour, particularly in executive aspects of attentional processing. Such control mechanisms serve to optimize performance when complex sequences of behaviour are required or when pre-potent responses need to be inhibited in order to achieve a later goal. This paper examines the nature of the cognitive control processes that contribute to executive functioning, the neural circuitry underpinning such processes and the distinct and separable contributions of the monoamine and cholinergic transmitter systems that modulate PFC function. Data will be presented from two rodent paradigms; namely the 5-choice serial reaction time task, which assesses executive aspects of visuo-spatial attention and a delay-of-reward paradigm, which assesses aspects of impulsivity. The results reveal dissociable functions of distinct fronto-striatal subregions and serotonergic receptor subtypes in attention, impulsivity and inhibitory response control as well as important differences in the behavioural contingencies that specifically affect noradrenaline, dopamine, serotonin and acetylcholine release in the PFC. The relevance of these findings to the pathophysiology and treatment of schizophrenia and attention-deficit hyperactivity disorder will be discussed. This work was supported by the Wellcome Trust and an MRC Center Grant in Clinical and Behavioral Neuroscience.

DISSOCIATING TIME AND EVENT MEMORY IN LABORATORY ANIMALS. McDonald, M. P. Department of Pharmacology and Program in Neuroscience, Vanderbilt University, Nashville, TN 37232-0325 USA. Delayed conditional discrimination (DCD) tasks used with primates and rodents differ in that primates are generally asked to discriminate between novel and familiar stimuli, whereas rodents are exposed to the same stimuli on every trial. Thus rodents must discriminate which stimulus they have seen more recently, i.e., a temporal discrimination rather than an event discrimination. We used the interval between choice on the present trial and sample presentation on a previous trial (Choice- S_B interval) as an index of temporal discrimination. Intertrial intervals (ITIs) were long (36 sec.) or short (4 sec.), and the retention interval was held constant at 6 sec. Presentations of the S_B sample occurred with one, two, or three S_A sample presentations intervening before the choice on the current trial. Using this design, some Choice- S_B intervals were independent of ITI duration or number of intervening trials (S_A presentations). In this way we can dissociate interference resulting from 1) short ITIs, 2) intrusion from previous trials, and 3) intrusion from short Choice- S_B intervals. Results demonstrate no difference in choice accuracy between long and short ITIs. There was a significant effect of intervening trials, but only on trials with short ITIs. The effect of increasing Choice- S_B interval was largest and independent of ITI or number of intervening trials. These results show that event and time memory interact in this DCD task, such that intrusion of information from previous trials depends largely on the amount of time that has elapsed since presentation of the conflicting information, and to a lesser extent on how many trials with concordant information have intervened.

COGNITION TESTING IN MICE. Baron, S. CNS Pharmacology. Pfizer Global R&D. Ann Arbor, MI 48105. With the recent use of genetically modified mice (GEMM) there has been a revival in the interest in mouse behavior. Mouse breeds (strains) were very popular at the beginning of the 20th century (Silver, 1995), and much of the use of mice used in early genetic studies were conducted on a lab-by-lab basis and were not readily available to the general scientific community. Behavioral studies were reported in the late 1920's; indeed BF Skinner wrote on the inheritance of maze behavior in mice (Skinner, 1929). Many of the studies examined the abilities of mice to learn maze tasks and later, the acquisition of operant responses. More recently, the sophistication of mouse behavioral assays has increased and allowed for the examination of complex cognitive behaviors and by employing GEMM there has been a further elucidation of the genetics and neurobiology of cognition. In this presentation I will discuss some of the species-specific phenotypes and recent and novel behavioral approaches focusing on complex cognitive behaviors in mice. Additionally, I will discuss important considerations, such as background genetics, in the study of genetics and neurobiology of cognition in mice.

10:30-12:00 **Oral Session 3: Learning and Memory.**

DEVELOPMENTAL EXPOSURE TO 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) LEADS TO CHANGES IN GENE EXPRESSION DURING ADULTHOOD IN RATS Skelton, M.R.1; Williams, M.T.2; Vorhees, C.V.1 1Div. of Dev. Biol & 2Pharmacol Res Center, Cincinnati Children's Res Found, Cincinnati, Ohio. Exposure to MDMA from postnatal (P) day 11-20, a period of hippocampal development analogous to third trimester human development, causes learning and memory deficits when the animals are tested in adulthood. The learning and memory deficits appear to be independent of concurrent monoamine deficiencies, therefore a novel approach was taken to identify possible mechanisms responsible for the learning and memory deficits. The hippocampi of adult (P60) animals treated from P11-20 with either MDMA (20mg/kg x 2 per day) or saline were hybridized to Affymetrix microarrays containing approximately 8,800 genes. Of the 8,800 genes screened, 33 genes were up-regulated significantly in MDMA treated animals (greater than 1.67 fold with a $p < 0.05$ between groups) and 5 genes were significantly down-regulated in MDMA treated animals (greater than 1.3 fold higher in the saline group with a $p < 0.05$). Several genes discovered in the microarray screening, including insulin-like growth factors and angiotensin converting enzyme, have been previously shown to have effects on learning and memory. The results of this study suggest the involvement of biochemical pathways leading to learning and memory deficits from early exposure to MDMA that would not have been anticipated using conventional approaches.

EFFECTS OF SUBSTANCE P AND NK1 RECEPTOR ANTAGONIST WIN 62.577 IN AMYGDALOID LEARNING MECHANISMS. Lenard, L.; Kertes, E.; Laszlo, K. Neurophysiology Research Group, Institute of Physiology, Pecs University Medical School, 7643 Pecs, Hungary. In the ventral pallidum and caudate-putamen complex substance P (SP) facilitates learning and has positive reinforcing effect. The amygdaloid body plays an important role in learning, memory and emotional behaviour. By means of immunohistochemical methods it has been revealed that this structure is rich in SP immunoreactive elements. SP has high affinity for neurokinin-1 (NK1) receptors and it can act on NK2 and NK3 receptors as well. In the rat central nucleus of amygdala (ACE) high density of NK1 receptors was found. WIN 62.577 is a nonpeptide NK1 receptor antagonist inhibiting the effects of SP. The aim of our experiments was to study the possible involvement of NK1 receptors in the effects of SP injected into the ACE. Wistar male rats were microinjected with 0.4 μ l of 10 ng SP, 100 ng SP or vehicle. In place preference paradigm significant reinforcing effect was found by 10 ng SP. In elevated plus maze 100 ng SP increased the time rats spent on the open arms and increased the number of excursions into the end arms indicating an anxiolytic profile. In water maze test post trial injection of 100 ng SP improved performance over controls. These effects of SP could be eliminated by prior treatment with WIN 62.577. Our results show that in the ACE 1) SP has positive reinforcing effect and facilitates learning in water maze task, 2) SP has anxiolytic effect in elevated plus maze, 3) these effects are mediated via NK1 receptors. *This work was supported by OTKA T034489, ETT 354/2000 and by the Hungarian Academy of Sciences.*

HIPPOCAMPAL MEDIATION IN AUDITORY PERCEPTUAL LEARNING. Orduña, I.; *Mercado III, E. & Gluck, M.A. Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ 07102 USA; *University at Buffalo, State University of New York, Buffalo, NY 14260 USA. The hippocampus has been shown to play a critical role in many learning and memory paradigms. A computational model developed by Gluck and Myers (1993) proposes that the hippocampus modifies cortical representations of sensory event to facilitate learning, and that it is particularly critical in the differentiation of sensory events. Discrimination learning in humans and other mammals has been shown to lead to improvements in the differentiation of the trained stimuli. Gluck and Myers' model (1993) predicts that such learning requires hippocampal processing. To examine how the hippocampus mediates learning about complex stimuli, we trained intact and hippocampal-lesioned rats to discriminate periodic, frequency-modulated sounds, using a two-alternative identification task. We then tested rats' ability to classify novel sounds with acoustic features similar to those they experienced during training. Our results show that rats with hippocampal damage can learn to discriminate complex sounds and associate them with distinct

responses, but that they learn the task in ways that differ from intact rats. These findings suggest that the hippocampus is involved in the adaptive processing of complex sensory events.

ESSENTIAL ROLE OF LEPTIN IN HIGHER BRAIN FUNCTION Oomura, Y.; Aou, S.; Li, X.; Hori, N.; Wayner, M. J.; Armstrong, D. L. Dept. Physiol., Faculty of Med., Kyushu Univ., Fukuoka, Japan, Public Health, New York Univ., Albany, N. Y., Dept. Biology, Univ. Texas, San Antonio, TX. U.S.A. Physiological increases of leptin in the rat brain facilitate emotional and spatial learning and memory associated with enhancement of long-term potentiation (LTP) as well as calmodulin kinase II (CaMKII) activity in hippocampal CA1 neurons. Zucker rats and db/db mice have abnormal leptin receptors and display impaired spatial learning and memory accompanied by a lack of hippocampal LTP and also low CaMKII activity. Ob/ob mice have normal leptin receptors but do not produce leptin with a normal molecular structure. Ob/ob mice also display impaired spatial learning and memory. Approximately one third of ob/ob mice show short-term potentiation but not LTP. When 50 μ g/kg/day leptin was applied iv for three weeks spatial learning and memory recovered normally. Body weight and food intake remained at original levels. LTP was not affected by leptin treatment. CaMKII activity is currently being determined. These results support an essential role for leptin in higher brain function.

THE EVERCHANGING CELLS OF WHALES. Mercado III, E. Dept. of Psychology. University at Buffalo, SUNY, Buffalo, NY 14260 USA. Auditory cortical neurons in adult mammals have dynamic response properties. For example, experience with behaviorally relevant acoustic events can rapidly change auditory sensitivities in cats, rats, bats and humans. Humpback whales must attend to behaviorally relevant acoustic events throughout their lives. During winter months, when humpbacks aggregate to breed, males produce long structured sound sequences called songs. The organization and spectrotemporal features of songs change yearly, such that songs from the current year always differ from songs produced in previous years. All singers within a particular region produce highly similar songs each year, suggesting that whales change their songs together. How might the annual reorganization of spectrotemporal features of songs be reflected in the auditory sensitivities of humpbacks? Recent comparative evidence from experiments with adult rats shows that changing the relevance of complex sounds through discrimination training or by pairing sound presentation with electrical stimulation of the basal forebrain can radically change the response properties of auditory cortical neurons. The area of cortex responsive to such sounds can be greatly increased and the responsiveness of neurons to these sounds can be significantly enhanced. It seems likely that humpback audition is at least as adaptable as audition in rats. If so, auditory cortical representations in humpback whales would be expected to reorganize annually in parallel with the reorganization of songs.

1:15-3:15 Symposium 5: Role of neurosteroids in the pharmacology of ethanol.

ETHANOL-STIMULATED INCREASES IN NEURO-ACTIVE STEROIDS IN BRAIN ARE DERIVED FROM ENDOCRINE ORGANS. Purdy, R.H.; Vallée, M.; O'Dell, L.E.; Alomary, A.A.; Fitzgerald, R.L.; Koob, G.F. Dept. of Neuro-pharmacology, The Scripps Research Institute, La Jolla, CA 92037 and Veterans Affairs Medical Center, San Diego, CA 92161 USA. The stress response to acutely administered ethanol has become a well-documented genetic marker for the predisposition to alcoholism in men. The common GABA A-type receptor for alcohol and neuroactive steroids suggests that these steroids might mediate alcohol effects. Accordingly, alcohol-related change in the rodent brain of levels of neuroactive steroids, such as allopregnanolone, has been recently proposed as a novel mechanism of action for alcohol. The purpose of this work was to investigate the impact of an acute administration of alcohol on the concentrations of the neuroactive steroids testosterone (T), DHEA, pregnenolone (PREG), allopregnanolone (ALLO) and allotetrahydrodeoxycorticosterone (alloTHDOC) in plasma and frontal cortex of adult male rats. Gas chromatography and negative chemical-ionization mass spectrometry was used to measure steroid levels in partially purified tissue extracts. We found that there was a marked increase of T, PREG, ALLO and alloTHDOC in plasma and frontal cortex 30 and 60min after acutely administered alcohol (2g/kg, i.p.; BAL=200mg/dL) relative to control rats. However, these alcohol-induced steroid changes were not observed in any ADX/GDX animals. Overall, these results demonstrate that the endocrine response to acutely administered alcohol is due to steroid biosynthesis in adrenal and gonadal tissue.

SOCIAL ISOLATION INCREASES THE STEROIDOGENIC EFFECT OF ETHANOL IN THE RAT BRAIN. Biggio, G.; Dazzi, L.; Serra, M. Department of Experimental Biology University of Cagliari. Social isolation of rats for 30 days immediately after weaning which results in marked decreases in cerebrocortical and plasma concentration of neuroactive steroids, greatly increases the sensitivity of rats to the steroidogenic effect of acute stress and ethanol. In fact, the percentage increases in brain and plasma concentration of pregnenolone, progesterone, 3 α , 5 α -TH PROG and 3 α , 5 α -TH DOC were markedly greater in isolated rats treated with ethanol (1 g/kg i.p.) or acute stressful stimuli than in group-housed animals. The previous demonstration that isolated rats exhibit increased self administration of ethanol together with the evidence that in these animals steroidogenesis is more sensitive to both acute stress and acute ethanol suggests the possible synergistic action among stress, ethanol and neuroactive steroids in modulating the functional activity of specific neuronal populations, such as the

mesocortical and mesolimbic dopamine pathways, involved in the modulation of addictive effects of ethanol. Consistent with this conclusion injection of progesterone (5 mg/kg i.p., once a day/5 days) increased the brain content of 3 α , 5 α -TH PROG and potentiated the biphasic effect of acute ethanol on dopamine output in the rat prefrontal cortex and nucleus accumbens. Both these effects are abolished by the 5 α - reductase inhibitor finasteride (25 mg/kg s.c.). Given that finasteride abolished also the enhancement of 3 α , 5 α -TH PROG elicited by both stress and ethanol while potentiating the stress-induced increase in cortical dopamine output, our results suggest that 3 α , 5 α - TH PROG might play a crucial role in modulating the action of ethanol on the activity of neurons that contribute to a vulnerability to alcohol abuse. The synergistic action of ethanol and 3 α , 5 α - TH PROG in the modulation of central dopaminergic neurons might help to clarify the neurochemistry of ethanol addiction.

MODULATION OF BRAIN NEUROACTIVE STEROID BY ENDOGENOUS AND EXOGENOUS g-HYDROXYBUTYRATE, A PUTATIVE THERAPEUTIC AGENT FOR ALCOHOL DEPENDENCE Concas, A.; Porcu, P.; Sogliano, P.; Gibson, M.K.*; Gupta, M.*; Biggio, G. Dept. Expt. Biol., Univ. of Cagliari, Cagliari, Italy, * Dept. Molec. Med. Genetics, Oregon Health Sci. Univ., Portland, OR, USA. g-Hydroxybutyrate (GHB), a naturally occurring compound derived from g-aminobutyric acid (GABA), has been proposed as an effective drug in the treatment of alcohol withdrawal syndrome and in the control of alcohol consumption and craving. It has been recently shown (Neuropharmacology, 42:782, 2002) that GHB shares with ethanol the capability to enhance the brain and plasma concentrations of the neuroactive steroids allopregnanolone (AP) and THDOC, two potent endogenous positive allosteric modulators of the GABA_A receptors. To further characterize the mechanism involved in the GHB-induced increase in the concentrations of neuroactive steroids we examined the effects of GHB in adrenalectomized-orchietomized rats (Adx-Orx). The acute administration of GHB (500 mg/kg, i.p.) resulted in a marked increase of progesterone, AP and THDOC levels in the cerebral cortex and plasma of sham-operated rats, while failed to affect the concentrations of these compounds in Adx-Orx rats, suggesting that GHB, like ethanol (World J Biol Psychiatry, 3:87, 2002), increases the brain and plasma neuroactive steroid concentrations through the activation of the hypothalamic-pituitary-adrenal axis. Moreover, we investigated the effect of chronic treatment with GHB (500 mg/kg i.p. twice a day for 10 days) on the cerebrocortical and plasma concentrations of progesterone, AP, and THDOC. The chronic treatment with GHB failed to affect basal levels of these hormones 48 h after the last drug administration, while a challenge administration of GHB (500 mg/kg, i.p.) similarly to ethanol (2 g/kg, i.p.) still increased markedly the cerebrocortical and plasma concentrations of progesterone, AP and THDOC, indicating that chronic treatment with GHB failed to induce tolerance to the effect of this drug and cross-tolerance to the effect of ethanol on the brain and plasma concentrations of these steroids. A new line of mutant mice deficient in succinate semialdehyde dehydrogenase, which display ataxia, develop generalized seizures and have significantly elevated brain GHB levels associated with a down regulation of GHB and GABA receptors in the cerebral cortex and hippocampus, has been recently generated (Nat. Genetics, 29:212, 2001). In these knockout mice we observed a significant lower brain concentration of progesterone and allopregnanolone with respect to wild-type mice. All together, these results provide new insight into the mechanisms for the GHB-induced increase in the brain neurosteroids levels which might help to clarify the anti-alcohol effects in alcohol-dependent subjects of this drug.

INTERACTION BETWEEN ENDOGENOUS ALLOPREGNANOLONE LEVELS AND ETHANOL CONSUMPTION. Finn, D.A.; Sinnott, R.S.; Long S.L.; Matthews, S.D.; Tanchuck, M.A.; Phillips, T.J. Dept. of Behavioral Neuroscience, Oregon Health & Science Univ. and Dept. of Veterans Affairs Medical Center, Portland, OR 97239 USA. The neuroactive steroid allopregnanolone (ALLOP) possesses positive motivational effects and ethanol (EtOH)-like discriminative stimulus effects. While ALLOP is a potent positive modulator of GABA_A receptors, EtOH interacts with multiple receptor systems and one effect of EtOH is to potentiate GABA_A receptors. It is not known if similar GABAergic mechanisms influence the positive motivational properties of EtOH and ALLOP. Thus, the present experiments investigated the modulatory effect of ALLOP on EtOH preference drinking and the potential contribution of endogenous ALLOP levels to this effect. Administration of ALLOP (10 mg/kg, ip) significantly increased limited access EtOH consumption of a 10% EtOH solution in male 129/J mice. ALLOP pretreatment (3.2, 10 or 17 mg/kg) also significantly increased limited access EtOH consumption of a 5% and 10% EtOH solution in male, but not female, C57BL/6J (B6) mice. Mice consuming the 10% EtOH solution were more sensitive to the modulatory effect of ALLOP than were animals consuming the 5% EtOH solution. In a separate study, the effect of limited access EtOH drinking on brain ALLOP levels was assessed in male and female B6 mice. EtOH consumption of a 10% solution significantly increased brain ALLOP only in male B6 mice. Overall, these findings indicate that ALLOP can increase consumption of preferred and non-preferred EtOH solutions and that there are sex differences in the modulatory effect of ALLOP on EtOH drinking and in the effect of EtOH drinking on endogenous ALLOP. Supported by USPHS grants AA12439 & AA10760 from NIAAA and the Dept. of Veterans Affairs.

STEROID NEUROGENESIS IS NECESSARY FOR ETHANOL-INDUCED COGNITIVE IMPAIRMENTS. Douglas B. Matthews¹, Sayaka Tokunaga¹, Janelle Silvers¹ and A. Leslie Morrow². ¹Department of Psychology, The University of Memphis, Memphis TN 38152; ²Bowles Center for Alcohol Studies, The University of North

Carolina, Chapel Hill, NC 25799. Acute ethanol administration alters hippocampal function as evidenced by impairments in spatial memory and changes in single unit hippocampal neurophysiology. Ethanol also increases hippocampal and cortical levels of the endogenous neurosteroid allopregnanolone to pharmacologically relevant levels. Finally, blockade of allopregnanolone biosynthesis by finasteride pretreatment blunts ethanol-induced increases in allopregnanolone levels and blocks ethanol induced decreases in the spontaneous neural activity of medial septal neurons. Given that the medial septum is critical for hippocampal function, this suggests that ethanol-induced increases in allopregnanolone levels might be a mechanism by which ethanol alters hippocampal function. Recently, we have demonstrated that both acute ethanol and acute allopregnanolone administration selectively impair spatial memory and alter single unit hippocampal neurophysiology. Chronic ethanol exposure produces tolerance to ethanol's spatial memory impairments and eliminates ethanol-induced increases in hippocampal allopregnanolone levels. Finally, pretreatment with finasteride prevents ethanol-induced decreases in spontaneous neural activity in hippocampal pyramidal neurons and blocks ethanol-induced spatial memory impairments. These data suggest that ethanol-induced elevation of hippocampal allopregnanolone content is one mechanism by which ethanol impairs spatial memory.

DISCRIMINATIVE STIMULUS EFFECTS OF NEUROSTEROIDS AND ETHANOL IN MICE, RATS AND MONKEYS. Grant, KA; Rogers LM; Purdy RM; Shannon E E. Dept. of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC 21157-1083 USA. The behavioral pharmacology of neurosteroids assessed in drug discrimination procedures using mice, rats and monkeys as subjects and ethanol or pregnanolone (3a,5b P) as the discriminative stimulus will be reviewed. Several findings have implications for these endogenous substances influencing ethanol-related behaviors. Briefly, substitution of the neurosteroids for ethanol occurs at circulating blood steroid concentration of 1 mg/ml. Endogenous neurosteroid levels appear additive to exogenous neurosteroid administration in producing discriminative stimulus effects. The discriminative stimulus effects of the neurosteroids that are similar to ethanol are blocked by the partial GABAA inverse agonist Ro 15-4513, with affinity estimates in the low micromolar (high nanomolar) range. Species differences are found in the substitution pattern of the isomers 3a,5b P, 3a,5a P, or 3b,5b P for the discriminative stimulus effects of ethanol, with rats but not monkeys showing ethanol-like effects of 3b,5b P. Rats trained to discriminate 3a,5b P show extremely similar stimulus effects of this neurosteroid compared to ethanol, however the cross-substitution pattern was not found in DBA/2J inbred mice. Overall, the data set suggest that neurosteroids have robust influences on the discriminative stimulus effects of ethanol, that these effects are mediated by the GABAA receptor system and that species and individual differences profoundly effect the interaction between ethanol and neurosteroids to influence behavior.

3:30-4:30 Keynote Speaker: Ann Kelley.

CORTICO-STRIATAL-HYPOTHALAMIC NETWORKS AND MOTIVATION FOR FOOD: INTEGRATION OF COGNITION, REWARD AND ENERGY. Kelley, A.E. Department of Psychiatry and Neuroscience Training Program, University of Wisconsin-Madison, Madison, WI 53719. One of the greatest current threats to public health in the developed world is obesity. In the U.S. nearly half a million people die prematurely each year from obesity-related illnesses. The abundant availability of calorically dense foods such as fats and sweets in modern Western diets is largely responsible for this epidemic. Neuroscience research can make critical contributions to the further understanding and treatment of this problem. Traditionally, major focus has been directed to the hypothalamus, and rightly so given its crucial role in energy balance and food intake. However, much less is known about how the hypothalamus functions within its associated networks that integrate other factors involved in appetite, such as sensory factors, emotional processing, decision-making, and learning. Our laboratory has been particularly interested in the role of neurotransmitter systems within the nucleus accumbens, a brain region implicated in natural reward processes as well as addiction, in the control of food motivation and intake. We have examined local GABAergic, dopaminergic and opioid peptide systems as well as the influence of input and output structures such as the amygdala and lateral hypothalamus. Our work with a number of different behavioral paradigms has shown that these neurochemical systems play specific and differentiable roles in different aspects of food seeking and food intake. The influence of both central and basolateral amygdala as well as lateral hypothalamus in regulating accumbens reward mechanisms appears particularly critical. We propose that the nucleus accumbens integrates information related to cognitive and emotional processing with hypothalamic mechanisms mediating energy balance. This system as a whole enables complex hierarchical control of adaptive ingestive behavior. Supported by the National Institute on Drug Abuse.

Sunday, April 27:

8:00-10:00 Symposium 6: Dissecting behavior with molecular genetics.

MARKER-ASSISTED SELECTION OF A NEUROBEHAVIORAL TRAIT RELATED TO BEHAVIORAL INHIBITION IN THE SHR STRAIN, AN ANIMAL MODEL OF ADHD. Mormede, P.; Moneva, E.; Bruneval, C.; Moisan, M.-P. Neurogenetics and Stress, INRA – University Bordeaux 2, Institut Francois Magendie, 33077 Bordeaux France. The search for the molecular bases of neurobehavioral traits in Spontaneously Hypertensive Rats (SHR), an animal model of Attention Deficit Hyperactivity Disorder, led to discovery of two quantitative trait loci related to locomotor activity in the center of the open field (Ramos et al., *Molecular Psychiatry*, 4: 453, 1999). In the present study, rats from an F2 intercross between the SHR and Lewis strains were selected for breeding based on their genotype at these two loci. We thus obtained two groups of F3 animals, a ‘high line’ in which rats have the alleles increasing the trait and a ‘low line’ with the trait-lowering alleles. The data obtained in a variety of novel environments show that the lower locomotor activity displayed by the low line in the center of the open field is not due to a low activity in general, but results from an inhibition of locomotor activity in aversive environments. However, this line difference is not attributable to a classical ‘anxiety’ factor as measured in the elevated plus maze, because the open arms behaviors were not different between lines. Conversely, the high line also showed a deficit in prepulse inhibition of the acoustic startle reflex. Altogether, the present data show that the two loci previously described in a SHR x Lewis intercross as related to the activity in the center of the open field are indeed involved in behavioral inhibition, a trait typical of ADHD. The marker-based selected lines described here are a unique tool for the study of the neurobiological bases of this trait.

GENETIC DISSECTION OF ETHANOL-RELATED BEHAVIORS IN RATS DERIVED FROM HIGH- AND LOW CONSUMING LINES. Jones, B. C.; Terenina, E.; Moisan, M.-P.; Mormède, P. Department of Biobehavioral Health, The Pennsylvania State University, University Park, PA 16802, USA and Institut François Magendie, Laboratoire de Neurogénétique et Stress, 33077 Bordeaux FRANCE. The recent development of a rat line that drinks large quantities of alcohol (HEP) has provided a unique opportunity for studying alcohol-related behaviors as they relate to measures of activity and reactivity. This was accomplished by breeding these animals with the WKY rat, well-known for low ethanol consumption. Multivariate behavioral analysis revealed that in F2 animals, alcohol consumption was nearly autonomous in females, while in males, consumption of low concentration of ethanol was related to anxiety-like behavior. Genetic analysis of chromosomal polymorphic markers revealed a QTL with a LOD score of 7.6 on chromosome 4 associated with consumption of 5% (v/v) ethanol. Genomic inspection showed this marker to be closely associated with the NPY gene. NPY has been shown by others to be related to ethanol consumption, so it is a reasonable candidate gene. Other QTL were discovered for saccharin drinking, elevated plus maze and open-field behaviors. Marker-assisted selection for F3 animals that were homozygous in both directions for the marker revealed a robust association of this marker with alcohol consumption and saccharin and quinine drinking, open-field behavior and plus-maze performance. The QTL method is a powerful technique to generate hypotheses concerning the relatedness among what may seem to be unrelated behavior and neurobiological measures. It is invaluable in ascertaining common, genetic-based mechanisms.

KNOCKOUT/CONGENIC STRAINS AS TOOLS FOR MAPPING BEHAVIORAL TRAITS IN THE MOUSE. Flaherty, L.; Bolivar, V.J.; Cook, M.N. Genomics Institute, Wadsworth Center, 465 Jordan Road, Troy, NY 12180 and University at Albany, Albany, NY 12201. We have used knockout/congenic strains to map several behavioral traits in the mouse. These are convenient tools for obtaining congenic strains that isolate single quantitative trait loci (QTL). Since most knockout strains of mice are also C57BL/6J (B6) knockout/congenics, i.e. they not only have an ablated gene but also have a short flanking chromosomal region derived from the 129 strain that surrounds the ablated gene, they can be used to map genes surrounding the ablated locus that differ between B6 and 129. Thus, we have tested a number of knockout/congenic strains for behavioral traits. These include knockouts of IL10, Fcgr3, CD4, CD8a, Drd3, Selp, CD28, IL6, CD3z, Tcrd, and Igl-5. Some of these knockout/congenic strains show highly significant differences in behavior from their inbred partners. We are now in the process of confirming these behavioral QTLs by breeding studies. We are also determining whether these differences are due to the ablated gene itself or to the flanking 129 genetic material. Traits that we have studied so far include open field activity, intersession habituation, contextual fear conditioning, and stereotypy.

TRANSCRIPTOME TO BEHAVIOR: GENE EXPRESSION PROFILING OF THE γ PKC NULL MUTANT MOUSE. Radcliffe, R. A.; Bowers, B. J.; Smith, A.; and Wehner, J. M. Department of Pharmaceutical Sciences, University of Colorado Health Sciences Center, Denver, CO 80262, USA and Institute for Behavioral Genetics, University of Colorado, Boulder, CO 80303, USA. A knockout of the gamma isoform of protein kinase C (γ PKC) was made by Abeliovich *et al.* (*Cell*, 1993) to study its role in learning and memory. In addition to showing mild learning deficits and impaired long-term potentiation, we have shown that the γ PKC knockouts were mildly ataxic,

less sensitive to the anxiolytic and sedative effects of ethanol, showed increased ethanol preference, were more behaviorally impulsive, and were impaired in the development chronic ethanol tolerance. While it is likely that some or all of those behavioral effects were due, at least in part, to a direct effect of the deleted gene (*i.e.*, γ PKC-mediated phosphorylation of key proteins), we postulate that the absence of γ PKC caused alterations in the regulation of many genes and that this effect on gene regulation contributed to the modified behaviors. To test this, we conducted gene expression profiling experiments in brains of the knockout mice using the Affymetrix GeneChip system. In a simple comparison of gene expression in the cerebellum of adult knockout vs. wild type mice, over 200 genes and ESTs were found to be up- or down-regulated. The genes fell into five basic functional categories: extra- and intracellular signaling; structural/intracellular transport; transcription factors; cell cycle/growth regulation; and apoptosis. Most striking were the effects on apoptosis-related genes with pro-apoptotic genes being generally up-regulated in the knockout and anti-apoptotic genes down-regulated. This observation has led to an interesting hypothesis that we are currently pursuing: that γ PKC is a central modulator of the pro-apoptotic effects of various drugs of abuse including ethanol. This putative role of γ PKC may contribute to the effects of the knockout on ethanol-related behaviors.

10:30-12:00 Oral Session 4: Genetic and neural injury models.

DISSECTING ALLELE-DEPENDENT MOTOR AND SLEEP BEHAVIOR IN A MOUSE LACKING TWO POTASSIUM CHANNELS. R.H. Joho, F. Espinosa, A. McMahon, G.A. Marks*, Ctr. Basic Neuroscience and *Dept. Psychiatry, UT Southwestern Medical Center, Dallas, Texas 95390-9111. Kv3.1 and Kv3.3 are high-threshold voltage-gated K⁺ channels that are widely, but not exclusively, co-expressed in the CNS including in the thalamus, basal ganglia and cerebellum, *i.e.*, areas implicated in the control and modulation of arousal states and motor activity. The Kv3.1- and Kv3.3-single mutants showed some physiological changes (Chan, 1997; Joho et al., 1999; Porcello et al., 2002; Macica et al., 2003), and initial studies suggested correspondingly subtle behavioral alterations (Ho et al., 1997; Sánchez et al., 2000). In contrast, the Kv3.1/Kv3.3-double mutant displays dramatic phenotypic alterations that include ataxia, myoclonus, tremor, alcohol hypersensitivity, increased motor activity and stereotypy, and severely disordered sleep (Espinosa et al., 2001). Exploiting the fact that Kv3.1 and Kv3.3 channels are not completely co-expressed throughout the entire brain, we have generated mice carrying different numbers of null alleles resulting in different K⁺ channel expression patterns. Studies of these mice revealed that loss of both Kv3.1 alleles correlates with constitutive hyperactivity and increased stereotypy. In contrast, the absence of both Kv3.3 alleles causes myoclonus and altered olivocerebellar circuit properties. Extension of these studies may allow us to identify regions of brain dysfunction that correlate with the altered behavior of particular K⁺ channel mutants. Supported by grants from NIH (NS42210 to RHJ and HL64277 to GAM), the Myoclonus Research Foundation (RHJ), and the Restless-Legs-Syndrome Foundation (FE).

GENETIC CORRELATIONS OF GENE EXPRESSION WITH NEURO-BEHAVIORAL TRAITS IN A RECOMBINANT INBRED MAPPING PANEL. ¹Chesler, E.J.; ²Wang, J.; ¹Lu, L.; ¹Qu, Y.; ²Manly, K.; ¹Williams, R.W. ¹Dept. of Anatomy & Neurobiology and Center for Genomics & Bioinformatics. Univ. of Tennessee Health Science Center, Memphis TN. ²Roswell Park Cancer Institute, Buffalo, NY. Genetic correlation analysis uses associations of phenotypes in similar or identical genetic background to evaluate shared genetic mediation of traits. The BXD/Ty recombinant inbred lines are an isogenic strain set made from re-inbred cross progeny of C57BL/6J and DBA/2J strains. They have been widely characterized on numerous, predominantly behavioral traits. Gene expression was assayed in these mice using the Affymetrix U74Av2 Murine GeneChip. Previously reported BXD/Ty strain phenotypes were obtained from the literature and from personal communication with authors. Associations of these phenotypes with expression levels of the thousands of transcripts on Affy arrays were calculated using Spearman's rank correlations. The results are available in our public database at <http://webqtl.roswellpark.org>. This Internet resource provides mapping of gene transcription and other complex traits using a high-density marker panel. The correlation of phenotypic values of gene expression and other traits can be used to narrow down the many hundreds of genes in a quantitative trait locus (QTL) to a handful of promising candidates for further evaluation. However, correlated transcripts need not reside in QTL regions. Transcription regulatory QTLs for highly correlated genes may also be the site of genetic variation responsible for behavioral variation. The assembly of data for the study of shared trait mediation will cumulatively enhance the utility of these strains as a behavior genetic resource.

BEHAVIORAL AND NEUROCHEMICAL EFFECTS INDUCED BY SUBCHRONIC EXPOSURE TO 40 PPM TOLUENE IN RATS. Berenguer P., Soulage C., Perrin D., Pequignot J.M., Abraini J.H.. UMR CNRS 6551, « Neuronal cell death, Neuroprotection & Neurotransmission », Center CYCERON, Université de Caen, FRANCE. Chronic toluene inhalation at concentrations above occupational exposure limits (*e.g.*: 100 ppm, NIOSH) has been repeatedly shown to induce neurotoxic effects. In contrast, although few clinical and experimental data are available on the effects of toluene exposure at concentrations below occupational exposure standards, some of this data may

support adverse effects of long-term exposure to low toluene concentrations. To test this hypothesis, we investigated the neurobehavioral and neurochemical effects of 40 ppm inhaled-toluene in a rat model of 16-week subchronic exposure examining locomotor and rearing activities, adaptation/sensitization to narcosis produced by acute exposure to toluene at high concentration, tyrosine- and tryptophan hydroxylase activities and dopamine and serotonin turnovers in the caudate-putamen, nucleus accumbens, hippocampus, prefrontal cortex and cerebellum. Our results mainly show that subchronic exposure to 40 ppm toluene significantly resulted in a sensitization to toluene-induced narcosis, a decrease in rearing activity, and alterations in dopamine and serotonin transmissions. This demonstrates that subchronic toluene exposure at low concentration may lead to adverse changes in neurobehavioral and neurochemical functioning, and further questions in a Public Health perspective the actual neurotoxic potential of toluene and other organic compounds, since deficits in functioning are generally viewed as precursors of more serious adverse effects.

INFLUENZA INFECTION OF THE RAT BRAIN IN MODELING ABNORMAL BRAIN AND BEHAVIOR DEVELOPMENT. Pletnikov, M.; Rubin, S; Skapik, J; Moran, T.H.; Carbone, K. Dept. of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD 21205, CBER/FDA, Bethesda, MD 20892. Influenza infection has been associated with a number of neurodevelopmental disorders, including schizophrenia. Here, we present the preliminary study of neurobehavioral abnormalities in two inbred rat strains, Fisher344 and Lewis, characterized by varying susceptibility to environmental insults. Virus replication, virus distribution, brain pathology and behavioral deficits were evaluated in rats at various time points after neonatal intracranial inoculation with influenza virus (A/WSN/33). Viral antigens were detected in meninges, subventricular zone and the external germinal layer of the cerebellum, with infectious virus being recovered from the brain during first six days post infection. Despite a brief period of virus infection in the brain, several strain-related neurobehavioral alterations were found when tested at postnatal day (PND) 30 and 60. While infected Lewis rats demonstrated a transient elevation in locomotor activity in the novelty test at PND 30, infected Fischer344 rats exhibited locomotor hyperactivity at PND 30 and 60. In addition, impaired habituation of the acoustic startle response was observed in infected Fischer344 rats at PND 60. Strain-related behavioral deficits could be explained by differences in brain pathology between the rat strains. In contrast to the lack of any gross histological alterations in the brain of infected Lewis rats, signs of moderate hydrocephalus were seen in infected Fischer344 rats. The present preliminary findings indicated the value of neonatal rat influenza infection model for studying the neuropathogenesis of "hit and run" viral damage and associated behavioral deficits. Supported by MH-48948.

ADMINISTRATION OF VARIOUS PSYCHOSTIMULANTS ON P11 CAUSES DIFFERENTIAL CHANGES IN CORTICOSTERONE AND MONOAMINE LEVELS 18 HOURS LATER: EFFECT OF METYRAPONE. Schaefer, T L; Williams, M T; Ehrman, L A; Gudelsky, G A; Vorhees C V. Cincinnati Children's Research Foundation and Univ of Cincinnati College of Medicine, Cincinnati, OH. We have studied the effects of neonatal administration of various psychostimulants, including the substituted amphetamines, to determine their effects on learning and memory in adult rats. A rank order of effects was found such that d-fenfluramine (d-FEN) and MDMA produced pronounced deficits on spatial and sequential learning, whereas methamphetamine (MA) only caused deficits in spatial learning. Cocaine (COC) and methylphenidate (MPH) had no effect on either type of learning. In the first study, either MA, MDMA, d-FEN, MPH, or COC at a concentration of 10 mg/kg or saline was administered subcutaneously every 2 hours for 6 hours on P11. 18 hours after the last dose, trunk blood, striatum, and hippocampus were collected. Corticosterone (CORT) levels remained increased significantly in animals treated with MA and d-FEN. In the striatum, 5-HT, 5HIAA, and DOPAC were reduced in animals treated with MA, MDMA, and d-FEN. In the hippocampus, 5-HT levels were reduced in MDMA and d-FEN animals. Minimal effects were seen in animals treated with COC and MPH. No changes in dopamine were seen following any drug. We repeated this study, excluding COC and MPH treatments, to determine if blockade of CORT by metyrapone during drug administration altered these effects. A paradoxical increase in CORT was observed in metyrapone treated MA and MDMA animals 18 hours after the last dose. Metyrapone produced minimal changes in monoamines. These studies are suggestive that changes in 5-HT and CORT during development may be involved in learning and memory deficits.

TRANSPLANTED STROKE ANIMALS DISPLAY NORMALIZED CEREBRAL BLOOD FLOW AND BBB PERMEABILITY DURING ONSET OF BEHAVIORAL RECOVERY. Lind, J1; Cheng, C1; Hadman, M1; Goodman, D1; Chopp, M5; Borlongan, CV1,2,3,4 1Dept Neurology and 2Inst Molecular Medicine Genetics, 3Sch Grad Stud, Med Coll GA; 4Augusta VAMC, Augusta GA; 5Dept Neurology, Henry Ford Health Sciences Center, Detroit, MI. Neural transplantation is an efficacious experimental treatment for neurological disorders, including stroke. Because interruption of cerebral blood flow and transient breakdown of blood brain barrier (BBB) are closely associated with stroke, we examined here neuroprotective effects of stem cell grafts on cerebral blood flow and BBB. Adult, male Sprague-Dawley rats underwent transient occlusion of middle cerebral artery (which produces striatal damage) and immediately received either intrastriatal infusion of stem cells (derived from human umbilical cord blood) or saline. Cerebral blood flow was monitored using Laser Doppler, while BBB permeability was

measured by Evans blue dye over a period of 2 weeks post-transplantation. Laser Doppler data revealed that transplanted stroke animals exhibited near normal cerebral blood flow (150 Perfusion Units) at a much earlier period post-transplantation (Day 7) compared to stroke animals that received saline (Day 12) ($p's < 0.05$). Similarly, Evans blue dye assay demonstrated that transplanted stroke animals displayed near complete BBB reconstitution at day 7 post-transplantation, whereas stroke animals that received saline still displayed a compromised BBB at this period. In a parallel study using the same surgical regimen, transplanted stroke rats showed near normal motor and cognitive performance, when evaluated in elevated body swing test and passive avoidance task, on day 7 post-stroke, at which time saline-infused stroke rats remained significantly impaired. These data suggest that restoration of cerebral blood flow and BBB permeability was achieved by stem cell grafts, and may contribute to the reported robust behavioral recovery in transplanted stroke animals.

All authors.

Abel, T.	16, 53	Campbell, T.	14, 45
Abraini, J.H.	11, 16, 19, 33, 51, 63	Canbeyli, R.	11, 31
Acik, A.	11, 31	Carbone, K.	19, 64
Adamec, R.	14, 43	Cardinal, R.N.	17, 57
Adamik, A.	14, 41	Carey, P.S.	15, 45
Adamo, A.	12, 34	Carey, R.J.	11, 33
Adamo, L.	12, 34	Carman, H.	8, 22
Aghajanian, G.	17, 55	Caron, M.	12, 36
Agmo, A.	13, 38	Casarrubea, M.	12, 34
Aksoy, A.	11, 31	Chandra, D.	16, 51
Al Banchaabouchi, M.	10, 11, 27, 34	Chen, G.	8, 9, 24, 25
Alomary, A.	18, 59	Cheng, C.	20, 64
Anticevic, A.	15, 49	Cheng, S.-Y.	10, 26
Aou, S.	18, 59	Chesler, E.J.	19, 63
Armstrong, D.L.	10, 18, 30, 59	Chévere, I.	10, 29
Augustsson, H.	8, 23	Choeiri, C.	11, 30
Baker, S.L.	13, 15, 40, 45	Chopp, M.	20, 64
Balogh, S.A.	16, 54	Concas, A.	18, 60
Baran, B.	11, 31	Conti, M.	12, 34
Baron, S.	17, 58	Cook, M.N.	19, 62
Barreto, J.	8, 15, 22, 49	Copeland, A.L.	16, 53
Barreto-Estrada, J.	15, 49	Corretjer, G.	8, 15, 22, 49
Barreto-Estrada, J.L.	8, 22	Coscina, D.	13, 39
Becker, L.A.	15, 49	Crawley, J.N.	13, 38
Bekkedal, M.	16, 51	Crescimanno, G.	12, 34
Belzung, C.	8, 23	Crites, G.	13, 41
Berenguer, P.	19, 63	Crooke, J.	13, 41
Berger-Sweeney, J.	15, 48	Crusio, W.E.	8, 23
Bernardo, A.	9, 24	Cryan, J.F.	13, 41
Berry, R.B.	16, 51	Cuyno, C.	15, 50
Bethea, J.	17, 55	Dale, D.	15, 49
Bielajew, C.	13, 15, 40, 46	Dalley, J.W.	17, 57
Biggio, G.	18, 59, 60	Darrah, M.	9, 15, 24, 47
Blanchard, D.C.	8, 15, 23, 50	David, H.N.	11, 16, 33, 51
Blanchard, R.J.	8, 15, 23, 50	Dazzi, L.	18, 59
Blanco-Centurion, C.	16, 50	De Souza Silva, M.A.	14, 44
Bloomer, R.	12, 35	Delgado, C.	14, 44
Bodfish, J.W.	12, 37	Dere, E.	14, 44
Bolivar, V.J.	19, 62	Dettling, A.C.	13, 40
Booze, R.	8, 22	Diaz-Trujillo, A.	16, 52
Booze, R.M.	7, 8, 21, 22	Dogra, S.	8, 9, 24, 25
Bordelon, J.R.	16, 53	Dolezal, A.	11, 32
Borlongan, CV.	20, 64	Drucker-Colín, R.	16, 53
Bothe, G.	16, 53	Dunnett, S.	11, 31
Bowers, B.J.	16, 19, 54, 62	Dunnett, S.B.	9, 25
Bramwell, J.	17, 55	Ehrman, L.A.	11, 19, 33, 64
Brenneman, D.	13, 41	Eilam, D.	12, 37
Brody, S.A. †	9, 16, 24, 54	Einat, H. †	8, 9, 24, 25
Brown, R.E.	9, 17, 24, 55	Ernisse, J.	16, 54
Brownlee, L.	15, 48	Erskine, M.S.	14, 15, 45
Bruchey, A.	9, 24	Espinosa, F.	19, 63
Bruckman, W.J.	11, 33	Evans, J.	12, 35
Bruneval, C.	19, 62	Fazio, G.	12, 34
Bruno, J.P.	9, 12, 24, 35	Feldon, J.	11, 13, 32, 40
Calamandrei, G.	15, 48	Félix, J.	10, 11, 28, 34
Camacho, F.J.	9, 14, 24, 45	Fernandez, M.	14, 44
Cameron, N.	15, 45	Ferreira-Nuño, A.	15, 45

Fienberg, A.A.	17, 54	Jay, J.R.D.	9, 25
Finn, D.A.	18, 60	Jiménez, D.M.	11, 34
Fitzgerald, R.	18, 59	Joho, R.H.	19, 63
Flaherty, L.	19, 62	Jones, B.C.	19, 62
Fleming, S.M.	9, 24, 25	Jorge, J.C.	8, 14, 15, 22, 23, 44, 45, 49
Flores, G.	10, 28	Joshi, D.	13, 39
Fortis, A.	8, 22	Kelley, A.	18, 61
Fortis, Y.	8, 15, 22, 49	Kelly, C.	9, 15, 24, 47
Franck, L.	10, 30	Kelly, P.H.	10, 27
Frantz, K.J.	12, 36	Kelly, S.J.	15, 48
Garavan, H.	7, 21	Kentner, A.C.	13, 15, 40, 45
García, E.	8, 23	Kertes, E.	17, 58
Garcia-Corbea, E.	14, 44	Kinsley, C.H.	14, 45
Gasbarri, A.	10, 29	Klamer, D.	11, 32
Gatien, M.L.	12, 35	Klipec, W.D.	10, 11, 30, 32
Geiselman, P.J.	16, 53	Kobsa, S.	15, 49
Geistfeld, J.	16, 53	Kolker, D.E.	10, 29
Gendle, M.H.	7, 21	Konkle, A.T.M.	13, 15, 40, 45
Gerashchenko, D.	16, 50	Koob, G.	18, 59
Gerhardt, G.A.	7, 21	Kovacevic, A.	11, 32
Gerritts, M.A.F.M.	15, 48	Kumru, G.	11, 31
Geyer, M.	12, 35, 36	Kunkel, A.J.	15, 49
Geyer, M.A.	9, 11, 12, 14, 16, 24, 32, 36, 43, 54	Labarca, C.	16, 54
Gibson, M.K.	18, 60	Labault, J.	10, 29
Giorgi, M.	10, 29	Lambe, E.	17, 55
Glasper, E.R.	14, 45	Lambert, K.G.	14, 45
Gluck, M.	18, 58	Laszlo, K.	17, 58
Goodman, D.	20, 64	Lebron, K.	14, 43
Goodwin, S.B.	16, 52	Lecourtier, L.	10, 27
Grandy, D.	11, 32	Ledesma de la Teja, S.	16, 52
Grant, K.A.	18, 61	Lee, A.W.†	9, 17, 24, 55
Gray, J.	7, 21	Lehman-Masten, V.	12, 36
Green, E.	17, 55	Lehmann, M.L.	14, 45
Greengard, P.	17, 54	Lehmann-Masten, V.	11, 32
Gudelsky, G.A.	11, 19, 33, 64	Lenard, L.	17, 58
Guilarte, T.R.	15, 47	Lester, H.A.	16, 54
Gupta, M.	18, 60	Levitsky, D.A.	7, 21
Haas, H.L.	14, 44	Lewis, H.W.III	12, 37
Hadman, M.	20, 64	Lewis, M.H.	12, 37
Hamilton, D.A.	17, 56	Li, C.	15, 50
Haro, R.	16, 53	Li, J.-S.	17, 56
Hasselrot, U.	7, 8, 21, 22	Li, X.	18, 59
Henry, S.	12, 35	Lin, S.M.	14, 45
Hernández-Poudevida, P.	14, 42	Lind, J.	20, 64
Heyser, C.J.	17, 54	Lipton, S.A.	9, 16, 24, 54
Hipkens, S.	9, 24	Lisanby, S.H.	9, 10, 24, 30
Hoane, M.R.	11, 31	Liu, R.	17, 55
Hohmann, C.	15, 48	Lizardi, L.	14, 45
Hohmann, C.F.	15, 48	Logue, S.F.	16, 54
Holmes, A.	13, 38	Lombardi, T.	16, 53
Homanics, G.E.	16, 51	Long, S.L.	18, 60
Hori, N.	18, 59	Lorenzini, I.	14, 44
Huang, F.L.	10, 29	Low, M.J.	11, 32
Huang, K.-P.	10, 29	Lu, L.	19, 63
Hubbard, D.	8, 23	Lucas, L.A.C.	13, 38
Hudspeth, O.	7, 21	Luo, M.	13, 38
Huston, J.P.	7, 11, 14, 17, 21, 33, 44, 56	Mactutus, C.	8, 22
Isacson, R.L.	12, 37	Mactutus, C.F.	7, 8, 21, 22
Ishibashi, M.	16, 50	Maestriperieri, D.	8, 24
Jaenisch, R.	17, 55	Malatynska, E.	13, 41
Jarvis, N.	15, 48	Maldonado-Vlaar, C.S.	11, 34

Manji, H.K.	8, 9, 24, 25
Manly, K.L.	19, 63
Markham, C.	8, 23
Markham, C.M.	15, 50
Markou, A.	13, 40
Marks, G.A.	19, 63
Marrero, J.	14, 44
Martin, P.D.	16, 53
Matthews, D.B.	16, 18, 51, 52, 60
Matthews, S.D.	18, 60
Mazzola, C.	12, 34
McCurley, M.A.	13, 39
McDonald, M.	9, 10, 24, 26
McDonald, M.P.	10, 17, 26, 57
McDougle, F.	16, 51
McEwen, B.S.	14, 42
McGinnis, M.	15, 47
McGlothlan, J.L.	15, 47
McInturf, S.	16, 51
McMahon, A.	19, 63
McMillen, B.A.	13, 38
Means, L.W.	11, 31
Meas, S.	15, 47
Mejia, R.	11, 32
Menéndez, R.	11, 34
Mercado III, E.	18, 59
Mercado, E.	18, 58
Messier, C.	11, 30
Milad, M.R.	14, 42
Milewski, M.	13, 41
Miller, L.R.	10, 26
Mineur, Y.S.	8, 23
Modica A.	10, 29
Moisan, M.-P.	19, 62
Moneva, E.	19, 62
Morales-Otal, A.	15, 45
Moran, T.H.	19, 64
Morgan, R.E.	7, 21
Mormède, P.	19, 62
Morrow A.L.	16, 18, 52, 60
Moscip, T.D.†	9, 10, 24, 30
Moulder, J.K.	11, 34
Müller, C.P.	11, 33
Murphy, C.A.	11, 32
Nakanishi, N.	9, 16, 24, 54
Neal, J.L.	16, 53
Neijt, H.	10, 27
Nelson, C.L.†	9, 12, 24, 35
Newell, K.M.	12, 37
O'Dell, L.	18, 59
Olaghere-DaSilva, U.	9, 24
Ong, J.	12, 35
Oomura, Y.	10, 16, 18, 30, 50, 59
Orduna, I.	18, 58
Ortiz-Zuazaga, H.G.	10, 28
Otero, J.M.	11, 34
Otero-Corchon, V.	11, 32
Otsubo, Y.	16, 50
Owens, C.H.	17, 54
Ozcelik, S.	11, 31
Pacitti, C.	10, 29
Pagán, J.	10, 27, 28
Paredes, R.G.	9, 14, 24, 45
Park, A.	16, 53
Parker, G.	13, 39
Passetti, F.	17, 57
Paulus M.	12, 36
Paulus M.P.	12, 36
Pelletier, M.N.	17, 54
Peña de Ortiz, S.	10, 11, 27, 28, 29, 34
Péquignot, J.M.	19, 63
Pereira, L.	10, 27
Pérez, J.	10, 28
Pérez, R.	10, 27
Pérez-Acevedo, N.L.	8, 23
Perrin, D.	19, 63
Pezzulo, P.	12, 35
Phelix, C.F.	10, 30
Phillips, T.J.	18, 60
Pignatelli, M.	10, 27
Pita, I.	9, 25
Pletnikov, M.	19, 64
Pompili, A.	10, 29
Porcu, P.	18, 60
Portillo, W.†	9, 14, 24, 45
Powell S.B.	12, 36
Powell, S.	12, 36
Prado-Alcala, R.A.	16, 52
Prasol, D.J.	8, 23
Pryce, C.R.	13, 40
Puig-Ramos, A.	11, 33
Puopolo, M.	15, 48
Purdy, R.	18, 59
Purdy, R.M.	18, 61
Qu, Y.	19, 63
Quirk, G.J.	14, 42, 43
Radcliffe, R.A.	19, 62
Ralph-Williams, R.	11, 12, 32, 36
Ramos, D.L.	11, 34
Ramos, X.	10, 28
Rapp, R.	13, 41
Redding, C.	15, 48
Reid, L.D.	16, 52
Reid, M.L.	16, 52
Ren, K.	10, 28
Resch, G.E.	13, 39
Ricceri, L.	15, 48
Rios, M.	17, 55
Risbrough, V.	12, 35
Risbrough, V.B.	14, 43
Ritchie, G.	16, 51
Rivera, J.C.	14, 44
Robbins, T.W.	17, 57
Robles, Y.	10, 28
Rogers, L.M.	18, 61
Rojas, Y.	8, 22
Rose, J.	12, 36
Rosenthal, D.	13, 41
Rossi, J.	16, 51
Rubin, S.	19, 64
Rüedi-Bettschen, D.	13, 40
Ruocco, L.A.	10, 26, 27

Russig, H.	11, 32	Toscano, C.D.	15, 47
Ryan, D.H.	16, 53	Turchi, J.	17, 57
Saavedra, M.C.	13, 38	Vakulenko, M.	15, 47
Sackeim, H.A.	9, 10, 24, 30	Vallee, M.	18, 59
Sadile, A.G.	10, 26, 27	Vallone, D.	10, 26
Sah, R.	11, 33	van Ree, J.M.	15, 48
Saia, V.	12, 34	Vázquez, A.	10, 28
Salvatore, M.F.	7, 21	Vedder, M.	16, 53
Sanchez, M.A.	16, 52	Velázquez-Moctezuma, J.	15, 45
Sanders, B.J.	15, 49	Vidal-Gonzalez, I.	14, 42
Santa-Maria Barbagallo, L.	15, 45	Viggiano, D.	10, 26, 27
Santiago, G.S.	11, 33	Vivas-Mejía, P.	10, 28
Santini, E.	14, 42	Vorhees, C.	17, 58
Sarter, M.	9, 12, 17, 24, 35, 56	Vorhees, C.V.	11, 19, 33, 64
Sasaki, K.	16, 50	Wang, J.	10, 19, 28, 29, 63
Scattoni, M.L.	15, 48	Washington, K.	15, 48
Schaefer, T.L.	11, 19, 33, 64	Watson, K.	15, 48
Schallert, T.	9, 24, 25	Wayner, M.J.	10, 18, 30, 59
Schellinck, H.M.	9, 15, 24, 47	Weaver, S.A.	15, 47
Schneider, B.	10, 30	Wehner, J.M.	16, 19, 54, 62
Segarra, A.C.	11, 33	Welch, M.	8, 22
Serra, M.	18, 59	Welch, M.A.	7, 8, 21, 22
Serrano, C.	9, 25	Werner, J.L.	17, 54
Serrano, G.	14, 44	White, T.L.	7, 21
Shannon, E.E.	18, 61	Williams, M.	17, 58
Shiromani, P.J.	16, 50	Williams, M.T.	11, 19, 33, 64
Siesser, W.	10, 26	Williams, R.W.	19, 63
Siesser, W.B.	10, 26	Winstanley, C.A.	17, 57
Silva, A.J.	10, 29	Wojna, V.	9, 25
Silvers, J.M.	16, 18, 52, 60	Wolterink-Donselaar, I.G.	15, 48
Simpson, C.W.	13, 39	Wood, M.	16, 53
Sinnott, R.S.	18, 60	Woodlee, M.T.†	9, 24, 25
Skapik, J.	19, 64	Wrenn, C.C.	13, 38
Skelton, M.	17, 58	Wu, J.	10, 29
Sloan, H.	11, 31	Yang, M.	8, 23
Smith, A.	19, 62	Yapici, N.	11, 31
Smith, B.G.	10, 30	Yuan, P.X.	8, 9, 24, 25
Smith, J.	8, 22	Zhao, J.	9, 24
Snow, D.	8, 22		
Snow, D.M.	7, 8, 21, 22		
Sogliano, P.	18, 60		
Sorbera, F.	12, 34		
Soulage, C.	19, 63		
Spieler, R.E.	14, 44		
Staines, W.M.	11, 30		
Stanford, L.†	9, 15, 24, 47		
Strawderman, M.S.	7, 21		
Strupp, B.J.	7, 8, 21, 22		
Sullivan, T.	13, 38		
Sutherland, R.J.	17, 56		
Sutter, T.R.	16, 52		
Swithers, S.E.	13, 39		
Szechtman, H.	12, 37		
Takahashi, L.K.	15, 50		
Tanchuck, M.A.	18, 60		
Telegdy, G.	14, 41		
Terenina, E.	19, 62		
Terrace, H.S.	9, 10, 24, 30		
Theobald, D.E.	17, 57		
Tokunaga, S.	16, 18, 52, 60		
Topic, B.	14, 44		

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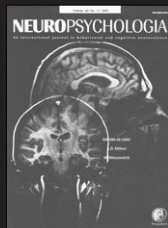
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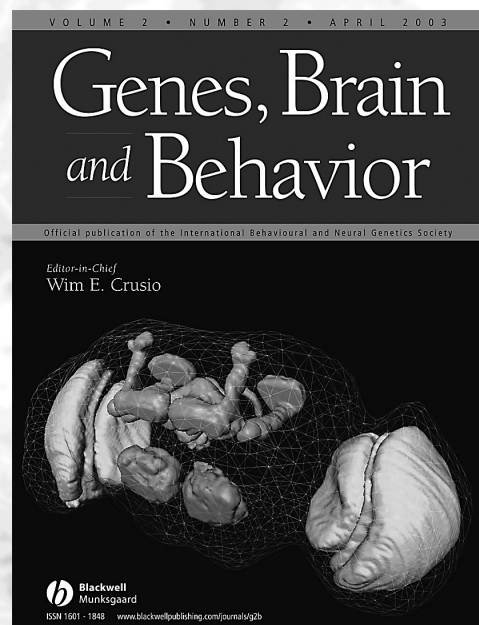
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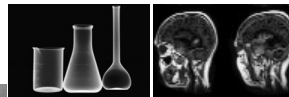
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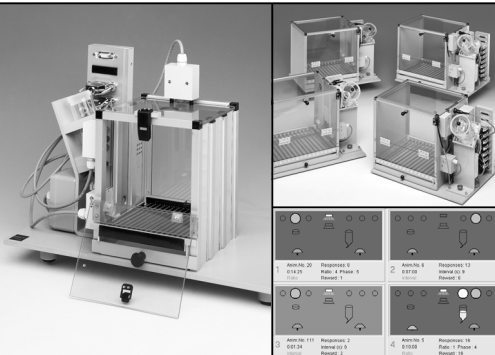
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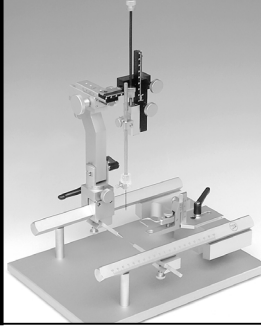
- The complete solution for drug research
- Fully computerized custom systems for rats and mice
- Includes ready-to-use trials such as FR, VR, PR, FI, VI, DRH and DRL
- Create your own schedules with the unique program composer!

VideoMot 2 - Video Activity System



- For all arenas including open field, water maze, elevated plus maze, radial maze...
- Outputs distance travelled, time spent, latencies, entries, speed, rotation
- With key-board event recorder

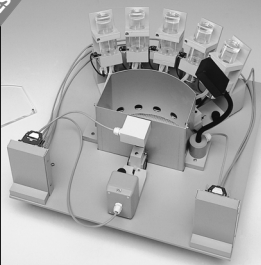
Stereotaxic Systems



- For all lab animals
- 3-dimension precision manipulator for left- & right-hand use
- Optional fine adjustment in the 3rd axis
- Choice of animal adapters, ear bars & accessories

NEW DESIGN

5-Hole-Box



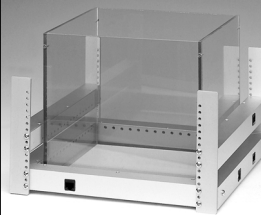
- Versatile attention testing system for rats & mice
- 5-choice serial reaction task
- Pellet feeder or liquid dispenser configuration
- Assess incorrect, correct & premature responses

Drinking & Feeding



- High-resolution food & liquid consumption data
- For all home cage sizes
- Custom configuration with up to 4 sensors per cage
- Detailed graphical & numerical evaluation

Motility Systems



- Study open field behavior or home-cage activity
- Variable box sizes and infrared sensor densities
- Vertical movement detection
- Detailed spatial & temporal analysis of locomotion

Contact us for other products and details.

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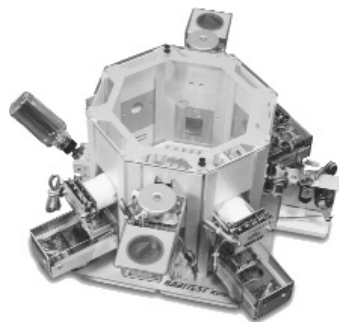
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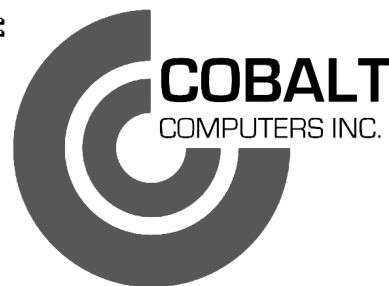
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Systems for Animal Sciences:

Behavior

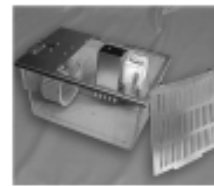
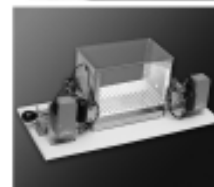
- 5-Choice Serial Task for Rats & Mice (9-Hole Systems)
- Classical Operant Systems
- Radial Arm Maze
- Monkey CANTAB
- Paw Reaching

Activity

- Rat & Mouse Activity Wheels With Living Chambers
- Rat & Mouse Forced Exercise Wheel Systems

Tissue Sectioning

- Integraslice
- Bath Coolers & Warmers

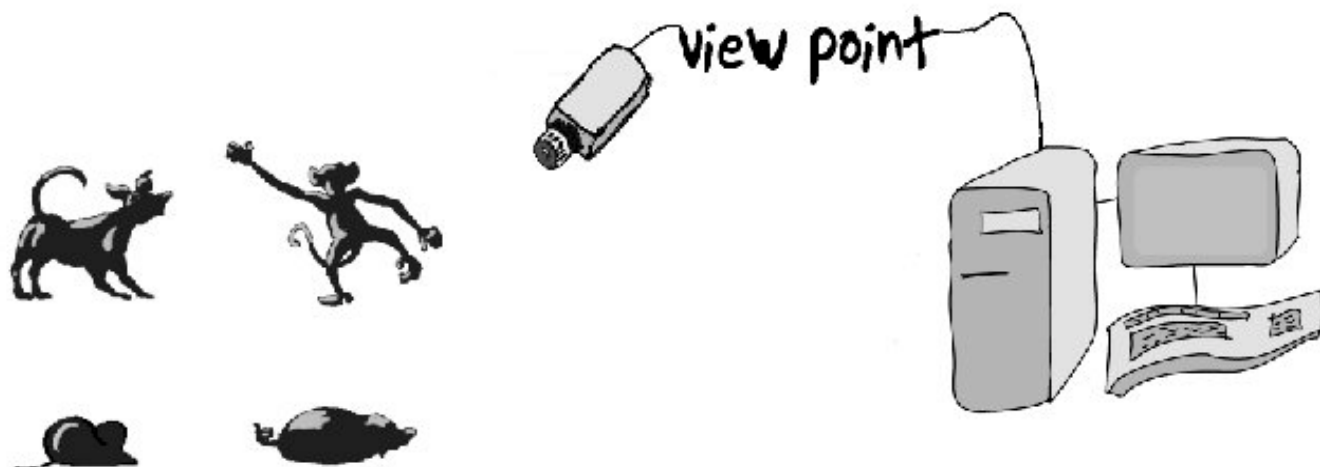


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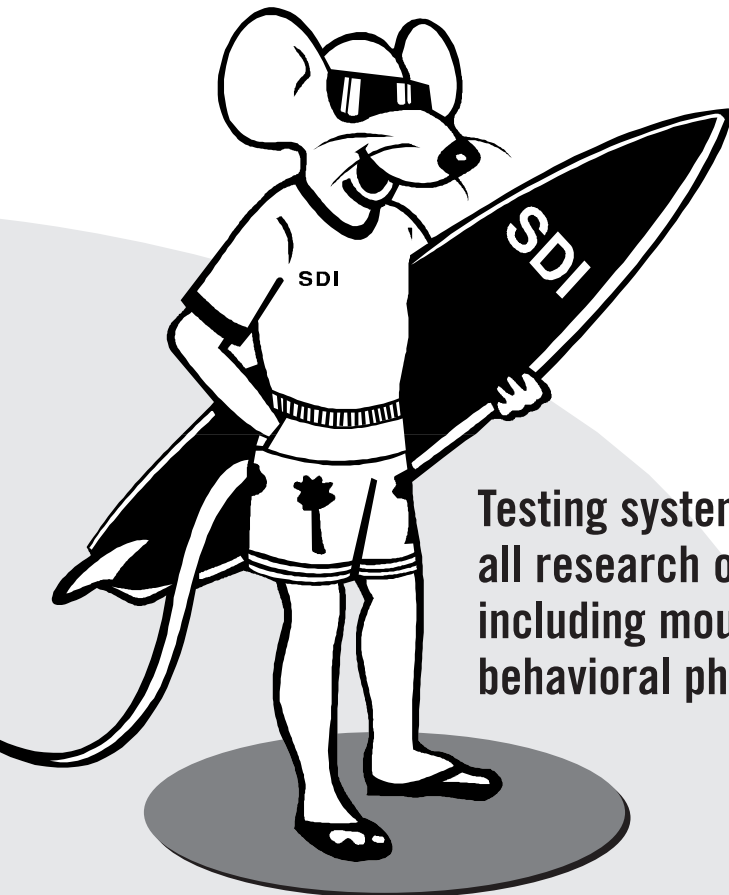
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Next IBNS Annual Meeting

June 16-20, 2004
Wyndham El San Juan Hotel
Key West, Florida