INTERNATIONAL BEHAVIOURAL AND NEURAL GENETICS SOCIETY

6th Annual Meeting
November 5-7, 2003
Hyatt Regency New Orleans Convention Hotel
New Orleans, Louisiana USA

Program

Sponsored by

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, USA
National Institute of Mental Health, National Institutes of Health, USA
National Institute on Aging, National Institutes of Health, USA
National Institute of Child Health and Human Development, National Institutes of Health, USA

Wednesday, November 5th

6:00-9:00pm	Registration	*Poydras AB – 2nd fl RCC*
7:00-10:00pm	Reception – hors d'oeuvres and cash bar	*Poydras AB – 2nd fl RCC*

Thursday, November 6th

7:00-7:45am	Thursday Speakers' Presentation Preparation *(please bring your PPT presentation to be loaded on our computer)*	*Loyola AB – Lower Level RCC*
7:00-8:30am	Continental Breakfast	*RCC Foyer - Lower Level*
8:15-8:30am	Opening Remarks	*Loyola AB – Lower Level RCC*
8:30-10:30am	Symposium Session I	*Loyola AB – Lower Level RCC*

Genetic influences on anxiety related behaviors: From mouse to monkey to man

Chairs & Organizers: Christina Barr & Tim Newman

DICBR/LCS Animal Center, National Institute on Alcohol Abuse and Alcoholism, NIH, Dickerson, Maryland, USA

Identifying genes that influence complex behaviors has become an increasingly important aspect of understanding the spectrum of etiological factors involved in the pathogenesis of neuropsychiatric disease. Both human and animal studies support a role for genes in the incidence of anxiety. While various anxiety-related traits are asserted to be under the influence of genes, gene association studies are often difficult to replicate. Of use to neurobehavioral genetics research is the use of animal models and the identification and definition of appropriate intermediate phenotypes. This symposium will discuss specific genes that may confer increased risk for anxiety and related disorders through the use of both animal models and human study populations. Presentations will include examination of the behavioral effects of serotonin transporter gene disruption in mice, with a focus on anxiety, aggression and behavioral responses to stress. In addition, the influences of various genetic polymorphisms on anxiety-related traits, including harm avoidance, neuroendocrine stress axis responses and low-voltage alpha resting EEG, will be addressed in non-human primate and human subjects. These polymorphisms will be further discussed in relation to complex behavioral traits, for example, alcohol consumption. Other relevant issues, such as sexually dimorphic effects of gene variation or gene by environment interactions, will also be addressed.

Behavioral phenotypes of serotonin transporter knockout mice; parallels with human anxiety and depression
Andrew Holmes, Laboratory of Behavioral Neuroscience, National Institute of Mental Health, NIH, Bethesda, Maryland, USA

The role of dopamine and MAOA candidate genes in influencing complex behavioral phenotypes: A model of alcohol consumption in the rhesus macaque
Tim Newman, DICBR/LCS Animal Center, National Institute on Alcohol Abuse and Alcoholism, NIH, Dickerson, Maryland, USA

Gene by environment interactions and the neuroendocrine stress axis: A non-human primate model of allostasis
Christina Barr, DICBR/LCS Animal Center, National Institute on Alcohol Abuse and Alcoholism, NIH, Dickerson, Maryland, USA

Genes, anxiety and alcoholism in humans
Mary-Anne Enoch, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland, USA

10:30-10:50am Coffee Break *RCC Foyer - Lower Level*
***Please arrange your posters on the boards provided in Loyola Room AB in preparation for the Poster Session this afternoon.*

10:50am -12:20pm Paper Session – Oral Presentations *Loyola AB – Lower Level RCC*

Overexpression of NTRK3 increases anxiety-like behavior and alters monoaminergic circuits in mice
Mara Dierssen, Program in Genes and Disease, Genomic Regulation Center, Barcelona, Spain

Impairment of APP transgenic mice in spatial and associative learning
*Christopher Janus, Centre for Research in Neurodegenerative Diseases, Univ of Toronto, Toronto, Canad**a***

Identification and quantitation of neurons expressing NR1 transgenes that modifies behavior, from HSV-1 vectors injected into the hippocampus
Diana Jerusalinsky, Institute of Cell Biology and Neuroscience, School Medicine, Univ of Buenos Aires, Buenos Aires, Argentina

Altered responses to ethanol in mice lacking functional N-type calcium channels
Philip Newton, Ernest Gallo Clinic and Research Center , Univ of California, San Francisco, Emeryville, California, USA

Gene expression profiles of GABAA α1 subunit-deficient mice: comparison of two knock-out models
Igor Ponomarev, Waggoner Center for Alcohol and Addiction Research, Univ of Texas at Austin, Austin, Texas, USA

Glutamate receptors and long-term memory in *C. elegans*
Catharine Rankin, Dept of Psychology & Brain Research Centre, Univ. of British Columbia, Vancouver, British Columbia, Canada

12:20-1:30pm Lunch (your own arrangement)

1:30-3:30pm Symposium Session II *Loyola AB – Lower Level RCC*

The molecular basis of drug reward: Gene knockout studies

Chair & Organizer: F. Scott Hall
Molecular Neurobiology Branch, National Institute on Drug Abuse, NIH, Baltimore Maryland, USA

The study of gene knockouts has lead to recent advances in our understanding of the genetic basis of drug reward. Many of the findings from these studies have been quite surprising; for instance, cocaine retains its rewarding effects in dopamine transporter (DAT) knockout mice indicating a polygenic basis of cocaine reward. The members of this panel (Ichiro Sora, S. Barak Caine, Rafael Maldonado and F. Scott Hall) have all made significant recent contributions to this literature, and the purpose of this symposium is to summarize their recent work and how this generally affects our understanding of the molecular basis of drug reward, and how such work shall proceed in the near future. Dr. Hall will discuss recent studies of cocaine reward using the conditioned place preference (CPP) paradigm in multiple gene knockouts, a strategy that was necessitated by the failure of any of the single monoaminergic transporter gene knockouts to eliminate cocaine reward. Such studies are also some of the first attempts to examine gene-gene interactions behaviorally in such a specific manner. Dr. Sora will discuss his recent studies examining extracellular dopamine and serotonin release using in vivo microdialysis in gene knockout mice. In particular, this data examined strains of knockout mice with normal or enhanced cocaine reward, DAT KO and SERT KO mice respectively, and also the DAT/SERT double knockout mouse, which he found does not exhibit rewarding effects of cocaine in the CPP paradigm. Dr. Caine will discuss his studies of cocaine self-administration in dopamine receptor and monoamine transporter knockout mice. He will particularly address the surprising retention of cocaine reward in many of these strains. Dr. Maldonado will round out the symposium by discussing the rewarding effects of other drugs, including cannabinoids, nicotine and MDMA. He will discuss his findings in opioid receptor knockout mice and aspects of both reward and dependence.

The molecular basis of the behavioral effects of cocaine as revealed by gene knockout studies in mice
*F. Scott Hall, Molecular Neurobiology Branch, National Institute on Drug Abuse, NIH, Baltimore Maryland, US**A***

Molecular genetics of monoamine transporter: Psychostimulant effects on extracellular monoamines
Ichiro Sora, Tohoku Univ, Sendai and Tokyo Institute of Psychiatry, Tokyo, Japan

Evaluation of cocaine self-administration behavior in mice with targeted mutations of dopamine D1, D2 or D3 receptors or the dopamine transporter
*S. Barak Caine, McLean Hospital/Harvard Medical School, Alcohol and Drug Abuse Research Center, Belmont, Massachusetts, US**A***

Involvement of the endogenous opioid system in drug addiction
Rafael Maldonado, Faculty of Health and Life Sciences Univ Pompeu Fabra, Spain

3:30-4:00pm Coffee Break *RCC Foyer – Lower Level*

4:00-6:00pm Poster Session – cash bar *Loyola AB – Lower Level RCC*

6:00-6:45pm IBANGS Business Meeting *Loyola AB – Lower Level RCC*

Friday, November 7th

7:00-7:45am Friday Speakers' Presentation Preparation *Loyola AB – Lower Level RCC*
(please bring your PPT presentation to be loaded on our computer)

7:00-8:30am Continental Breakfast *RCC Foyer – Lower Level*

8:15-8:30am Opening Remarks *Loyola AB – Lower Level RCC*

8:30-9:30am Plenary Address *Loyola AB – Lower Level RCC*

Genetics of Rewarding and Aversive Effects of Ethanol
Christopher L. Cunningham
Portland Alcohol Research Center, Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon, USA

9:30-10:00am Coffee Break
***Please take down your posters from the boards in Loyola Room AB. The poster boards will be removed at 12:00 noon today.*

10:00am -12:00pm Symposium Session III *Loyola AB – Lower Level RCC*

The multifaceted roles of brain-derived neurotrophic factor in neuronal adaptations
Chair & Organizer: Robert Lipsky, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland, USA

BDNF is a member of the neurotrophin family of trophic factors. Neurotrophins are essential regulators of neuronal development, neuronal function and survival, and structural plasticity. It is released upon neuron activation and signals through its cognate receptor, TrkB, strengthening either excitatory or inhibitory signals. BDNF has been implicated in a number of mood disorders, including major depression and anxiety. Therefore, BDNF is a major candidate for developing neurotrophin-based therapeutics. This symposium focuses on the genetics and phenotypes associated with changes in BDNF expression.

Nucleotide sequence diversity in the 5' terminal exons and flanking sequences of the human brain-derived neurotrophic factor gene: Implications for hippocampal function
Robert Lipsky, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland, USA

BDNF signaling mediates the effects of dietary restriction on neurogenesis, neuronal survival and peripheral glucose metabolism
Mark Mattson, Laboratory of Neurosciences, National Institute on Aging, NIH, Baltimore Maryland, USA

Control of synaptic plasticity and behavior by BDNF: Study of mice with conditional knockouts
Alexei Morozov, Mood and Anxiety Disorders Program, National Institute of Mental Health, NIH, Bethesda, Maryland, USA

BDNF bridges the gap between NMDA receptor blockade and dopamine hyperactivity
Pierre Sokoloff, Unit of Neurobiology and Molecular Pharmacology, INSERM, Paris, France

The role of neurotrophins in the CNS drug action
Eero Castrén, Neuroscience Center, University of Helsinki, Finland

12:00-1:30pm Lunch (your own arrangement)

1:30-3:30pm Invited Talks – Outstanding Young Investigator Awardees *Loyola AB–LLRCC*

Functional variation in vasopressin 1a receptor gene structure within and between vole species predicts behavior.
Elizabeth Hammock, Center for Behavioral Neuroscience, Emory University, Atlanta, GA, USA

Novelty seeking and dopamine receptor polymorphisms in adolescence.
Noa Heiman, Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA

Novelty-seeking behaviors and alcohol preference in mice lacking alpha1G T-type Ca2+ channels.
Daesoo Kim, National CRI Centre for Calcium and Learning, Korea Institute of Science and Technology, Seoul, Korea

A glutamatergic basis for impaired ethanol-induced plasticity in Homer2 null mutant mice.
Karen Szumlinski, Physiology and Neuroscience, Medical Univ of South Carolina Charleston, SC, USA

3:30-4:00pm Coffee Break *RCC Foyer – Lower Level*

4:00-6:00pm Symposium Session IV *Loyola AB – Lower Level RCC*

Genotype-environment interactions in behavioral phenotyping: So what are we supposed to do about them?
Chair & Organizer: Neri Kafkafi, Maryland Psychiatric Research Center, University of Maryland, Baltimore, Maryland, USA

To elucidate pathways from specific genes to complex behaviors, assays of mouse behavior need to be valid, reliable and replicable across laboratories. While better standardization of housing and test parameters remains desirable, recent studies suggest that it is not likely to eliminate the interaction effect. The symposium will focus on several complementary approaches to this problem.

(In)stability of brain size and behavior over decades in different laboratories
Douglas Wahlsten, Dept. of Psychology, University of Alberta, Edmonton, Alberta, Canada

Identification of laboratory environment factors influencing a behavioral trait via computational analysis of a large data archive
*Jeffery S. Mogil, Dept. of Psychology, McGill University, Montreal, Quebec, Canad**a***

Designing better measures of behavior using a multi-lab database of raw data
Neri Kafkafi, Maryland Psychiatric Research Center, University of Maryland, Baltimore, Maryland, USA

Is this interaction good or bad? Mixed Model statistical analysis of multi-lab results
Yoav Benjamini, Dept. of Statistics and Operation Research, Tel Aviv University, Tel Aviv, Israel

6:00-6:15pm Closing Remarks *Loyola AB – Lower Level RCC*

7:00pm Cash bar opens in the banquet hall *Cabildo Room C - 2nd fl RCC*

7:30-10:00pm Banquet *Cabildo Room C - 2nd fl RCC*

Symposia and Poster Abstracts

Symposium Session I: Thursday, November 6th, 8:30 a.m.

Symposium Abstract:
Genetic influences on anxiety related behaviors: From mouse to monkey to man.
Chairs & Organizers: Christina Barr & Tim Newman
DICBR/LCS Animal Center, National Institute on Alcohol Abuse and Alcoholism, NIH, Dickerson, Maryland, USA
Identifying genes that influence complex behaviors has become an increasingly important aspect of understanding the spectrum of etiological factors involved in the pathogenesis of neuropsychiatric disease. Both human and animal studies support a role for genes in the incidence of anxiety. While various anxiety-related traits are asserted to be under the influence of genes, gene association studies are often difficult to replicate. Of use to neurobehavioral genetics research is the use of animal models and the identification and definition of appropriate intermediate phenotypes. This symposium will discuss specific genes that may confer increased risk for anxiety and related disorders through the use of both animal models and human study populations. Presentations will include examination of the behavioral effects of serotonin transporter gene disruption in mice, with a focus on anxiety, aggression and behavioral responses to stress. In addition, the influences of various genetic polymorphisms on anxiety-related traits, including harm avoidance, neuroendocrine stress axis responses and low-voltage alpha resting EEG, will be addressed in non-human primate and human subjects. These polymorphisms will be further discussed in relation to complex behavioral traits, for example, alcohol consumption. Other relevant issues, such as sexually dimorphic effects of gene variation or gene by environment interactions, will also be addressed.

Behavioral phenotypes of serotonin transporter knockout mice; parallels with human anxiety and depression.
Andrew Holmes, Laboratory of Behavioral Neuroscience, National Institute of Mental Health, NIH, Bethesda, Maryland, USA
Gene mutations and polymorphisms in proteins that regulate the brain monoamine systems, such as transporters and catabolic enzymes, are attractive candidate genes for emotional disorders given the weight of evidence implicating monoamines in these conditions. Evidence of a link between genetic variation the serotonin transporter (5-HTT) and depression and anxiety from recent human and primate work prompted the generation of 5-HTT (htt) knockout (KO) mice. Loss of 5-HT reuptake in 5-HTT KO mice causes reduced clearance of extracellular 5-HT and associated alterations in 5-HT neuronal firing and receptor function. Behavioral phenotyping of 5-HTT knockouts has thus far revealed a variety of abnormalities, including increased anxiety-like behaviors, hypoactivity, reduced aggression, and exaggerated responses to stressors. Certain phenotypic alterations in 5-HTT KO mice varied according to background strain, indicating epistatic interactions between the htt null mutation and background genes. Interactions between the htt null mutation and environmental stress have also been observed under certain conditions; with behavioral deficits occurring in 5-HTT KO mice in response to repeated, but not acute, stress. Given the unparalleled ability to control genetic and environment background in rodent studies, the 5-HTT KO mouse could provide a valuable model system to study how gene variants interact with one another, and with environmental adversity, in the etiology of mood and anxiety disorders.

The role of dopamine and MAOA candidate genes in influencing complex behavioral phenotypes: A model of alcohol consumption in the rhesus macaque.
Tim Newman, DICBR/LCS Animal Center, National Institute on Alcohol Abuse and Alcoholism, NIH, Dickerson, Maryland, USA
TK Newman1,2, CS Barr1,2, CC Parker3, SJ Suomi3, K-P Lesch4, D Goldman2, JD Higley1.
Identifying genes that influence complex behaviors has become an increasingly important aspect of understanding the spectrum of etiological factors contributing to inter-individual differences in animal model behavior. We discuss recent results from our lab investigating polymorphisms in the dopamine D1 receptor (DRD1) and MAOA genes in a study of ethanol consuming behavior in rhesus macaques. Five SNPs in the

5’ non-coding region of the DRD1 gene and a 3 allele VNTR in the promoter region of the MAOA gene were genotyped in subjects raised either with their mothers until six months of age, or in peer-only groups - an established model for early life stress. As adults they were subjected to a seven-week voluntary ethanol consumption experiment. Since variation in ethanol consumption is influenced by sex and rearing experience in our colony, we tested for both main effects and interaction between variables. DRD1 haplotypes were significantly associated with variation in alcohol consumption, with main effects of sex and rearing. This was driven by a single SNP (-111 T□G) with an interaction between sex, rearing and genotype, such that peer-reared males with the minor allele consumed the most ethanol. For MAOA (males only), peer-reared males with the high activity allele consumed the most ethanol. Our work demonstrates a potential role for both the DRD1 and MAOA genes in modulating behaviors linked with alcohol consumption, especially in the context of early environmental stress. 1Laboratories of Clinical Studies and 2Neurogenetics, NIAAA, 3Comparative Ethology, NICHD, National Institutes of Health. 4Clinical and Molecular Psychobiology, Department of Psychiatry and Psychotherapy, University of Würzburg, Würzburg, Germany.

Gene by environment interactions and the neuroendocrine stress axis: A non-human primate model of allostasis.

Christina Barr, DICBR/LCS Animal Center, National Institute on Alcohol Abuse and Alcoholism, NIH, Dickerson, Maryland, USA

CS Barr1, TK Newman1, RL Dvoskin1, CC Parker2, K-P Lesch3, D Goldman4, SJ Suomi2, JD Higley1.

It is thought that chronic activation of the neuroendocrine stress axis contributes to allostatic load (or, wear and tear) at the level of the brain. Various factors, including genetic or sex differences, experience, and lifestyle choices are also thought to contribute to allostatic load via their influences on physiologic pathways. We are interested in determining individual differences in vulnerability to stress as well as to dysregulated activity of the limbic hypothalamic pituitary adrenal (LHPA) -axis, as such differences may be markers for predisposition to stress-related disorders and may contribute to allostatic load in the brain. The nonhuman primate model is particularly useful for such studies since their environments can be controlled. We have demonstrated that macaques with genetic variation in the serotonin transporter gene promoter (rh5-HTTLPR) that have been exposed to early-life stress have exaggerated LHPA-axis responses to stress, particularly among females. Females exposed to early-life stress also have augmented LHPA-axis responses to alcohol. When given access to alcohol, these females, especially those carrying the rh5-HTTLPR s allele, show marked increases in their levels of consumption with successive exposures to alcohol. Newly-identified variants within the macaque CRH gene promoter will also be discussed, as polymorphisms within the CRH gene would be likely to influence neuroendocrine stress axis activity both following stress and exposures to ethanol. 1NIAAA DICBR, NIH, Clinical Studies, Primate Unit, Poolesville, MD, USA; 2NICHD, NIH, Laboratory of Comparative Ethology, Poolesville, MD, USA; 3Clinical and Molecular Psychobiology, Department of Psychiatry and Psychotherapy, University of Würzburg, Würzburg, Germany; 4NIAAA, NIH, Laboratory of Neurogenetics, Rockville, MD, USA.

Genes, anxiety and alcoholism in humans.

Mary-Anne Enoch, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland, USA

M-A Enoch, KV White, J Waheed, L Schwartz, K Young, K Xu, J Taubman, CR Harris, D Goldman.

Anxiety can be both advantageous (increased arousal and response to external stimuli) and detrimental, leading to self-medication with anxiolytics such as alcohol. Harm avoidance (HA), a subscale of the Tridimensional Personality Questionnaire, is a heritable dimensional measure of anxious temperament; the human counterpart of observed anxious behavior in rodents. We have looked at the relationship between anxious temperament, pathological anxiety (clinical anxiety disorders) and alcoholism in two independent community-ascertained populations; 280 U.S. individuals, largely Caucasian, and 384 individuals from a Plains American Indian tribe. In both samples, women had higher HA than men, including total groups, individuals without any psychiatric disorders and alcoholics. Anxiety disorders were significantly associated with higher HA in men but not in women. Further analyses suggest that elevated HA may predispose to alcoholism in women and mood disorders in men. We have found that the Met/Met genotype of the functional catechol-0-methyltransferase (COMT) polymorphism, Val158Met, is associated with anxious temperament, but not with anxiety disorders, in both groups of women. In our search for candidate genes for

alcoholism and anxiety we have focused on electrophysiological intermediate phenotypes. We have shown that low voltage alpha (LVA), a resting EEG phenotype that is more abundant in alcoholics with anxiety disorders, is associated with the Met/Met genotype of COMT Val158Met and also with the functional DRD2 – 141CIns/Del promoter polymorphism in both populations. In addition, we are focusing on the low and high amplitude P300 event-related potential that is associated with alcoholism and anxiety, respectively. Results of further candidate gene analyses will be presented, in particular for GABAA receptors. Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD, USA.

Paper Session – Oral Presentations: Thursday, November 6th, 10:50 a.m.

Overexpression of NTRK3 increases anxiety-like behavior and alters monoaminergic circuits in mice.
Mara Dierssen, Program in Genes and Disease, Genomic Regulation Center, Barcelona, Catalonia, Spain
M Dierssen1, M Gratacòs1, I Sahún1, M Martín2, X Gallego1, A Amador-Arjona1, MM de Lagrán1, P Murtra2, MA Pujana1, R Maldonado2, C Fillat1, X Estivill1,3.
The neurotrophin type 3 receptor(NTRK3) maps to a human chromosome 15 region postulated to be involved in anxiety disorders, and is the only neurotrophin receptor expressed in the locus coeruleus (LC). This genomic region is duplicated in panic patients, and thus a gene dosage effect could be proposed. A possible mechanism would be that increased dosage of NTRK3 would alter synaptic plasticity in the LC by changing local trophic support, and would produce abnormal function of catecholaminergic neurotransmitter systems leading to panic disorder. In order to evaluate this hypothesis, we have developed several lines of transgenic mice that overexpress NTRK3, under the control of the PDGFB promoter. Stereological analysis demonstrates that NTRK3 overexpression causes an increase in the volume of LC and in the number and density of tyrosine hydroxilase (TH) positive neurons in this region. TgNTRK3 mice showed an increased anxiety-like behavior in different tests and an enhancement of panic reaction in the mouse defense test battery (MDTB). Response to the panicogenic agent yohimbine, was paradoxical in TgNTRK3 brains, suggesting 2 adrenoreceptors deregulation. These results raise the possibility that overexpression of NTRK3 would be determinant for the development of panic disorder through the regulation of neural plasticity in specific monoaminergic circuits involved in the pathogenesis of this disorder and suggest a new pathogenetic mechanism via 2 adrenoreceptors deregulation. 1Program in Genes and Disease, Genomic Regulation Center-CRG, Barcelona Biomedical Research Park, E-08003 Barcelona, Catalonia, Spain, 2Unit of Neuropharmacology, Pompeu Fabra University, Barcelona Biomedical Research Park, E-08003 Barcelona, Catalonia, Spain and 3Unit of Genetics, Pompeu Fabra University, Barcelona Biomedical Research Park, E-08003 Barcelona, Catalonia, Spain. 2This work was supported by Spanish Ministry of Science (SAF2001-1231, SAF2002-00799) and Fundació Marató TV3. MML is recipient of a MICYT fellowship.

Impairment of APP transgenic mice in spatial and associative learning.
Christopher Janus, CRND, Univ. of Toronto, Toronto, Canada
Deposition of ß-amyloid peptide in the brain is a major pathological feature of Alzheimer's Disease. Transgenic mice (TgCRND8) encoding a double mutated allele of human APP genes (Swedish; KM670/671NL+Indiana; V717F) develop extracellular amyloid deposits in the hippocampus and forebrain and are impaired in spatial reference and working memory from 12 weeks of age onwards. In this study, 35-week old TgCRND8 mice with abundant amyloid brain pathology and non-transgenic (non-Tg) littermates were given a longitudinally administered battery of cognitive tests including: (a) a visible platform version of Morris water maze (MWM) test, (b) a reference memory MWM test, and (c) conditioned taste aversion (CTA) test (i.e. learning the association between novel taste and induced nausea). The results demonstrated that TgCRND8 mice exhibited greater variability of responses as compared to non-Tg littermates in all tests. In addition, they showed a significant impairment in escaping to cued and hidden escape platforms, as well as impairment in the association between novel taste of saccharine and LiCl-induced (i.p. injection) nausea. There was no significant association between performance in all 3 tests in non-Tg mice. In contrast, in TgCRND8 mice impaired performance in a cued version of MWM was significantly positively correlated with their impaired learning during CTA test. The scores of the two types of associative learning were not correlated with levels of amyloid beta in the brain. However, the impaired performance in the reference

memory MWM test was significantly positively correlated with both soluble and insoluble (formic acid extracted) forms of amyloid beta peptide.

Identification and quantitation of neurons expressing NR1 transgenes that modifies behavior, from HSV-1vectors injected into the hippocampus.

Diana Jerusalinsky, Institute of Cell Biology and Neuroscience, School Medicine, Univ of Buenos Aires, Buenos Aires, Argentina

V Cheli1,2, M Adrover1,3, C Blanco1, A Cornea2, G Sánchez1, N Colettis1, M Snitcofsky1, E Martín1, A Epstein3, D Jerusalinsky1

We have shown that the expression of NR1 and GFP transgenes from HSV-1 derived vectors injected into the dorsal hippocampus of adult Wistar rats, mainly happened into neurons, in a discrete region. The NR1 expression was reduced in primary cultures of neurons, and in the hippocampus of rats injected with a NR1 antisense expressing vector. They suffered an impairment in performance of both, an open field test for habituation to a new environment, and an inhibitory avoidance to a foot-shock; while rats injected with the vector expressing NR1 did not show significant differences compared to naive animals. These results - together with evidences previously reported- suggested that the NMDA receptor in the dorsal hippocampus participates in mechanisms leading to habituation, as well as in acquisition and/or consolidation of the inhibitory avoidance, since both tasks suffered serious impairements even after slight changes in the availability of the NR1 subunit. However we knew neither the area nor the identity of cells infected, and presumably responsible for those changes. The animals were injected with vectors expressing both NR1 sequences and GFP; brain slices were immunostained to identify neurons and glia, and the transgenes. The cells were identified and quantitated under confocal microscopy, using an ad hoc software. Our data showed that most of the infected cells are pyramidal or granule neurons in a restricted area under the injection, and that only a few astrocytes expressed GFP. The quantitation suggested that only about 8-10 % of the neurons in that region were affected. Hence, it would mean that a single gene transfer in just a few neurons -and a slight modification in the protein-, is enough to produce those significant alterations in learning and memory. 1IBC&N, Sch. Med., and Dept. Anat., Sch Vet., Univ. of Buenos Aires, Argentina, 2ONPRC-OHSU, Oregon, USA, 3Ctr. of Mol. & Cell. Genetics, Univ. Claude Bernard, Lyon , France. Supported by Guggenheim Foundation, Fogarty Tech. Assist. Grant (USA); CNRS/CONICET (France-Argentine), ANPCYT and Univ. Bs. As. (Argentine).

Altered responses to ethanol in mice lacking functional N-type calcium channels.

Philip Newton, Ernest Gallo Research Center, Department of Neurology, University of California San Francisco, Emeryville, CA, USA

PM Newton1, Orr CJ1, Shin HS2 Messing RO1.

N-type calcium channels are important for neurotransmitter release and are the target of many neuromodulators, including opioids and adenosine. Previous work in our laboratory has shown that acute ethanol treatment inhibits N-type calcium channel function, and that chronic ethanol vapor inhalation treatment increases the density of N-type calcium channels in the frontal cortex and hippocampus of mice. These data suggest that N-type calcium channels may be a molecular target for acute alcohol intoxication, and may also form part of the neuroadaptive changes that occur in response to chronic alcohol exposure. In order to test these hypotheses, we studied alcohol responses in mice lacking the alpha-1B subunit of N-type calcium channels. F1 hybrid (129SvJ x C57/BL6) male alpha-1B knockout mice showed a reduced preference for ethanol, both in two bottle choice and place preference assays. They showed a dramatically decreased sensitivity to ethanol in the loss of righting reflex assay, but a slightly increased sensitivity to ethanol-induced ataxia on the accelerating rotarod. Suprisingly, handling induced convulsion scores following chronic exposure to ethanol vapor were increased in the knockouts. Clearance of ethanol from the blood did not differ between genotypes. These data suggest that N-type calcium channels mediate some of the hypnotic and rewarding effects of ethanol. Upregulation of N-type calcium channels after chronic ethanol exposure may limit manifestations of alcohol dependence. 1Ernest Gallo Research Center, Department of Neurology, University of California San Francisco, Emeryville, CA, 94608 USA. 2National Creative Research Initiatives Center for Calcium and Learning, Korea Institute of Science and Technology, Seoul 136-791, Korea. This work was supported by funds provided by the National Institutes of Health, grant number AA08117.

Gene expression profiles of GABAA α1 subunit-deficient mice: comparison of two knock-out models.
Igor Ponomarev, Waggoner Center, University of Texas, Austin, TX, USA
I Ponomarev1, G Schafer1, YA Blednov1, GE Homanics2, RA Harris1.
The α1 subunit of GABAA receptors is a constituent of the major GABAA receptor subtype in the murine brain. Mice lacking this subunit demonstrate a number of physiological and behavioral alterations, including a marked ethanol-induced locomotor stimulation (Blednov et al. JPET 2003 Jan., JPET 2003 Mar.; Kralic et al., JPET 2003). The objective of the present study was to determine whether deletion of this gene in mutant mice produced changes in expression of other genes. Another objective was to compare gene expression profiles of two independently created GABAA α1 KO models. We used cDNA microarrays to examine expression profiles of GABAA α1 knock-out (KO) and wild type (WT) animals. Total RNA was isolated from cerebellum or midbrain region of KO and WT littermates. Genisphere ® 3DNA technology kit was utilized for reverse transcription, labeling and hybridization of the tissue cDNA on a glass slide containing ~16000 elements. Relative expression for each gene was calculated and averaged across 3-9 mice per genotype. Based on a two-sample t-test at $p<0.01$, about 1% of all detected genes were differentially expressed in two genotypes. Among the most substantial alterations in mutant mice was differential expression of midkine, a growth factor found in senile plaques of Alzheimer's patients. About 6% of all significantly detected genes were similarly regulated for the two KO models. We hypothesize that alteration in expression of some genes, such as GAP-43 and ARPP-21 may influence ethanol-related behaviors in KO mice. 1Waggoner Center, University of Texas, Austin, Texas, USA; 2 University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
Supported by the NIAAA INIA program (grants: AA13520, AA13518).

Glutamate receptors and long-term memory in C. elegans.
Catharine Rankin, Dept of Psychology & Brain Research Centre, Univ of British Columbia, Vancouver, British Columbia, Canada
C Rankin, J Rose, S Steidl.
Long-term memory in C. elegans depends on glr-1, a homologue of mammalian non-NMDA glutamate receptors, expressed on the interneurons of a mechanosensory circuit. Both mutations in glr-1 and an AMPA receptor antagonist blocked long-term memory. We used a genetic marker to visualize glr-1 expression in the interneurons of trained and untrained worms and a marker for vesicles to look for changes in the tap sensory neurons. Trained animals had less glr-1 expression than untrained animals; there was no difference in expression of the vesicle marker. Thus, long-term memory in C. elegans is dependent on glr-1 and involves post-synaptic but not pre-synaptic changes in gene expression. avr-14 encodes a a-type subunit of a glutamate-gated chloride channel (GluCls) expressed on the glutamatergic mechanosensory neurons of the tap-withdrawal response that synapse onto the command interneurons. The mutation selectively effects short-term habituation for shorter interstimulus intervals (ISIs; 10s and 30s) while not effecting habituation for long ISIs (45s and 60s). These results provide support for the hypothesis that in C. elegans there are multiple ISI-dependant short-term memory systems. avr-14 worms show long-term memory for habituation training comparable to wild-type controls when given distributed training and testing with a 60s ISI. avr-14 worms, unlike wild-type controls, also show long-term memory when trained and tested with a 10s ISI. Furthermore, long-term memory for this training protocol is protein synthesis dependant, as administering heat shock in between blocks of training blocks the formation of long-term memory. This suggests that in wild-type worms the presence of avr-14 blocks the conversion from short-term to long-term memory following training with short ISIs. Dept of Psychology & Brain Research Centre, Univ of British Columbia, Vancouver, British Columbia, Canada. Research supported by NSERC, CIHR and BCMCFH-HELP.

<u>Symposium Session II: Thursday, November 6th, 1:30 p.m.</u>

Symposium Abstract:
The molecular basis of drug reward: Gene knockout studies.
Chair & Organizer: F. Scott Hall
Molecular Neurobiology Branch, National Institute on Drug Abuse, NIH, Baltimore Maryland, USA

The study of gene knockouts has lead to recent advances in our understanding of the genetic basis of drug reward. Many of the findings from these studies have been quite surprising; for instance, cocaine retains its rewarding effects in dopamine transporter (DAT) knockout mice indicating a polygenic basis of cocaine reward. The members of this panel (Ichiro Sora, S. Barak Caine, Rafael Maldonado and F. Scott Hall) have all made significant recent contributions to this literature, and the purpose of this symposium is to summarize their recent work and how this generally affects our understanding of the molecular basis of drug reward, and how such work shall proceed in the near future. Dr. Hall will discuss recent studies of cocaine reward using the conditioned place preference (CPP) paradigm in multiple gene knockouts, a strategy that was necessitated by the failure of any of the single monoaminergic transporter gene knockouts to eliminate cocaine reward. Such studies are also some of the first attempts to examine gene-gene interactions behaviorally in such a specific manner. Dr. Sora will discuss his recent studies examining extracellular dopamine and serotonin release using in vivo microdialysis in gene knockout mice. In particular, this data examined strains of knockout mice with normal or enhanced cocaine reward, DAT KO and SERT KO mice respectively, and also the DAT/SERT double knockout mouse, which he found does not exhibit rewarding effects of cocaine in the CPP paradigm. Dr. Caine will discuss his studies of cocaine self-administration in dopamine receptor and monoamine transporter knockout mice. He will particularly address the surprising retention of cocaine reward in many of these strains. Dr. Maldonado will round out the symposium by discussing the rewarding effects of other drugs, including cannabinoids, nicotine and MDMA. He will discuss his findings in opioid receptor knockout mice and aspects of both reward and dependence.

The molecular basis of the behavioral effects of cocaine as revealed by gene knockout studies in mice.

F. Scott Hall, Molecular Neurobiology Branch, National Institute on Drug Abuse, NIH, Baltimore Maryland, USA

FS Hall1, J Drgonova1, M Goeb1, I Sora2, DL Murphy3, K-P Lesch4, LH Tecott5, R Hen6, GR Uhl1.

The surprising result that cocaine retains its rewarding effects in dopamine transporter (DAT) knockout mice has lead to the examination of the role of other monoamine system genes in cocaine reward. The first studies in following creation of the DAT knockout (KO) examined the role of the serotonin transporter (SERT) and the norepinephrine transporter (NET) in cocaine reward. Combination of DAT KO mice with SERT KO mice completely eliminated cocaine reward as assessed in the conditioned place preference (CPP) paradigm, while combination of the SERT KO with NET KO mice produced greatly enhanced cocaine reward. Furthermore, both NET and SERT blockers (nisoxetine and fluoxetine) produced significant conditioned place preferences in DAT KO mice, but not in WT mice. Thus, the role of NET and SERT appears to be different in WT and DAT KO WT mice. Overall, these studies indicate important interactions between monoaminergic system genes in cocaine reward, in particular between DA and 5-HT systems. A heterozygous deletion of the gene for brain derived neurotrophic factor (BDNF), which influences growth and differentiation of both DA and 5-HT systems, also reduces potency of cocaine in producing CPP. To add insights into the DA and 5-HT subsystems that influence cocaine rewarding and aversive features, the combined effects of transporter and receptor knockouts have now been examined,, including combination of the DAT KO mouse with deletion of the 5-HT 1B receptor, the DAT KO mouse with deletion of the 5-HT 1A receptor, and the SERT KO mouse with deletion of the DA D2 receptor. None of these combinations of knockouts eliminated cocaine reward, as was previously observed in the DAT/SERT KO mouse, however gene knockout of each of the 5-HT autoreceptors, 5-HT1A and 5-HT1B, produced increases in cocaine reward such as those observed in SERT KO mice. These provide further evidence for the important involvement of both DA and 5-HT system genes in the rewarding effects of cocaine. 1National Institute on Drug Abuse, NIH/DHHS, Baltimore, MD, USA; 2Tohoku University, Sendai, Japan; 3National Institute of Mental Health, NIH/DHHS, Bethesda, MD, USA; 4University of Wurzburg, Germany; 5University of California San Francisco, San Francisco, CA, USA; 6Columbia University, New York, NY, USA. Supported by funding from the NIDA IRP, NIH/DHHS, USA.

Molecular genetics of monoamine transporter: Psychostimulant effects on extracellular monoamines.

Ichiro Sora, Tohoku Univ, Sendai and Tokyo Institute of Psychiatry, Tokyo, Japan

I Sora1, 2, H Shen1, H Kobayashi1, FS Hall3, GR Uhl3.

Cocaine conditioned place preference is intact in dopamine transporter (DAT) knockout (KO) mice and enhanced in serotonin transporter (SERT) KO mice. However, this measure of cocaine reward is eliminated in double KO mice with no DAT and either no or one SERT gene copy. To help determine mechanisms underlying these effects, we examined basal and drug-stimulated extracellular dopamine (DA) and serotonin (5-HT) levels in microdialysates from nucleus accumbens (NAc), caudate putamen (CPu) and prefrontal cortex (PFc) of wildtype, homozygous DAT or SERT KO and heterozygous or homozygous DAT/SERT double KO mice which are differentially rewarded by cocaine. Cocaine fails to increase extracellular DA in NAc of DAT KO mice. By contrast, cocaine enhances dialysate dopamine in both CPu and PFC of DAT KOs. Additional deletion of SERT to DAT attenuates the cocaine-induced DA increases found in CPu, but not those found in PFC. The selective SERT blocker fluoxetine increases extracellular DA in CPu of DAT KO mice, while the selective DAT blocker GBR12909 increases extracellular 5-HT in CPu of SERT KO mice. Each of these findings adds pieces to the complex puzzle of the mediation of cocaine reward by monoaminergic systems. 1Tohoku University, Sendai, Japan; 2Tokyo Institute of Psychiatry, Tokyo, Japan; 3National Institute on Drug Abuse, NIH/DHHS, Baltimore, MD, USA.

Evaluation of cocaine self-administration behavior in mice with targeted mutations of dopamine D1, D2 or D3 receptors or the dopamine transporter.

S. Barak Caine, McLean Hospital/Harvard Medical School, Alcohol and Drug Abuse Research Center, Belmont, Massachusetts, USA

Much evidence suggests that the reinforcing effects of cocaine are related to blockade of the dopamine transporter and consequent increases in the binding of dopamine to postsynaptic dopamine receptors. Results from traditional behavioral pharmacology studies in rats and monkeys suggest roles for the dopamine D1, D2 and D3 receptors and the dopamine transporter in cocaine self-administration. We have compared operant responding maintained by food and cocaine injections in mice with targeted mutations of these different proteins and their wild type littermates. First, differences and similarities between cocaine self-administration behavior of the mutant strains and their wild type littermates will be summarized. Second, agreement and disagreement between findings from traditional pharmacological studies and those from studies in mice with targeted mutations will be reviewed. Third, emphasis will be placed on considerations other than the targeted mutation, including potential species and strain differences, compensatory mechanisms and other complications of interpreting findings from these studies of mice with targeted mutations. The objective of this presentation is to promote discussion regarding whether these gene targeting studies have increased our understanding of neural mechanisms that underlie cocaine's reinforcing effects, or not, and challenges for future studies.

Involvement of the endogenous opioid system in drug addiction.

Rafael Maldonado, Faculty of Health and Life Sciences Univ Pompeu Fabra, Spain

Several studies have shown functional relationships between the endogenous cannabinoid and opioid systems. We have investigated different acute and chronic responses induced by delta9-tetrahydrocannabinol (THC) in several lines of knockout mice deficient in opioid receptors. Acute THC pharmacological responses and physical dependence were not modified in knock-out mice with single deletion of mu, delta or kappa opioid receptors. However, the rewarding properties induced by THC were abolished in mu knockout mice, whereas the disphoric effects induced by a high dose of this compound were suppressed in kappa knockout mice. Functional activity of CB1 cannabinoid receptors was evaluated by the ability of WIN 55,212-2 to stimulate [35S]-GTPgS binding. Interestingly, this activity was decreased in the striatum in mu knockout mice and increased in the substantia nigra in delta knockout mice. To further investigate these interactions, we have also evaluated THC responses in double mu and delta opioid receptor knock-out mice. Antinociception and hypolocomotion induced by acute THC administration remain unaffected whereas the acute hypothermic effects were slightly attenuated in these double mutants. During chronic THC treatment, double knock-out mice developed slower tolerance to the hypothermic effects but the development of tolerance to antinociceptive and hypolocomotor effects was almost unaffected. The rewarding properties of THC were abolished in these double knock-out mice, and the somatic manifestations of THC withdrawal were also significantly attenuated, suggesting that a cooperative action of mu and delta opioid receptors is required for the entire expression of THC dependence.

Symposium Session III: Friday, November 7th, 10:00 a.m.

Symposium Abstract:
The multifaceted roles of brain-derived neurotrophic factor in neuronal adaptations.
Chair & Organizer: Robert Lipsky, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland, USA
BDNF is a member of the neurotrophin family of trophic factors. Neurotrophins are essential regulators of neuronal development, neuronal function and survival, and structural plasticity. It is released upon neuron activation and signals through its cognate receptor, TrkB, strengthening either excitatory or inhibitory signals. BDNF has been implicated in a number of mood disorders, including major depression and anxiety. Therefore, BDNF is a major candidate for developing neurotrophin-based therapeutics. This symposium focuses on the genetics and phenotypes associated with changes in BDNF expression.

Nucleotide sequence diversity in the 5' terminal exons and flanking sequences of the human brain-derived neurotrophic factor gene: Implications for hippocampal function.
Robert Lipsky, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, Maryland, USA
RH Lipsky, X Jiang*, AM Marini*, J Hoberman, E Westly, W Grant, K Xu.
There is growing interest in the brain-derived neurotrophic factor (BDNF) gene as a candidate for vulnerability to addictions and other psychiatric conditions. Although temporal and spatial patterns of BNDF gene expression during neurodevelopment of mice and rats have been mapped, little is known about transcriptional regulation of the human BDNF gene. Four promoters of the BDNF gene are known. The primary DNA sequences of these promoter regions are highly conserved between rats, mice, and humans and appear to be differentially transcribed in the brain, at least in the rat. The human BDNF gene is composed of four 5' untranslated exons (1-4), clustered on a 21.8 kb region of chromosome 11. Each BDNF transcript is initiated separately within the 5' flanking region from each of these untranslated exons. The primary transcripts are differentially spliced to a single 3' coding region, exon 5, which encodes the entire sequence for the mature polypeptide, located approximately 42 kb downstream of the cluster of untranslated exons. To better understand the complex regulation of BDNF, we used denaturing high performance liquid chromatography (dHPLC) to identify candidate sequence variants in PCR amplified products obtained from a panel of genomic DNAs from 480 unrelated individuals of diverse clinical and ethnic backgrounds. DNA sequence variants were confirmed by direct sequencing of PCR products. Using this approach, we identified two sequence variants in BDNF promoter regions and two variants in the exons 1 and 4. All of the variants were previously unidentified. We also determined the haplotype structure for a cluster of sites, including a functional promoter variant near the extreme 5' end and a missense variant in the 3' end of the gene, covering a physical distance of approximately 70 kb. Genotyping was performed using 5'-exonuclease assays in two populations: a Finnish population (N = 754) and a Southwest American Indian population (N = 505). There was no significant deviation from Hardy Weinberg Equilibrium in either population. D' was computed using the Pairwise program. The programs estimate maximum-likelihood haplotype frequencies from unphased diploid genotypes. On the basis of these haplotype frequencies, the level of linkage disequilibrium (LD) between each pair of sites was assessed using the D' measure of allelic association. LD was high (0.99) across the 3' end of the BDNF gene in each population, indicating that the region was contained in a single haplotype block. In addition, we have produced reporter constructs and are expressing them in neuronal cell lines in order to determine their role in BDNF gene expression. It is likely that these BDNF polymorphisms will exert specific effects on hippocampal function in humans. Section on Molecular Genetics, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, Rockville, MD, USA. *Department of Neurology and Neuroscience, Uniformed Services University of the Health Sciences, Bethesda, MD, USA.

BDNF signaling mediates the effects of dietary restriction on neurogenesis, neuronal survival and peripheral glucose metabolism.
Mark P. Mattson, Laboratory of Neurosciences, National Institute on Aging Gerontology Research Center, Baltimore, MD, USA

MP Mattson, W Duan, R Wan. Studies in this and other laboratories during the past 5 years have provided convincing evidence that dietary restriction (DR; reduced calorie intake or intermittent fasting) increases the resistance of neurons to injury and disease (Physiol. Rev. 82: 637-672.). Rodents maintained on DR regimen exhibit reduced neuronal damage and improved behavioral outcome on models of stroke, Parkinson's, Alzheimer's and Huntington's diseases. In addition, DR stimulates neurogenesis by promoting the survival of newly generated neurons. We have found that DR stimulates the production of brain-derived neurotrophic factor (BDNF) and stress resistance proteins including HSP-70 and GRP-78. Interestingly, our studies of mice with reduced BDNF levels and of huntingtin mutant mice suggest that BDNF signaling in the brain regulates peripheral glucose metabolism, and plays a central role in the abilities of DR to increase insulin sensitivity and protect neurons. We are currently investigating reciprocal interactions between BDNF and serotonin signaling in the brain in regards to their roles in neuronal plasticity and in aging and age-related disease processes. We are also working to develop novel preventative and therapeutic strategies for neurodegenerative disorders based upon dietary and pharmacological interventions that enhance BDNF and/or serotonergic signaling. Laboratory of Neurosciences, National Institute on Aging Gerontology Research Center, Baltimore, MD, USA.

Control of synaptic plasticity and behavior by BDNF: Study of mice with conditional knockouts.
Alexei Morozov, Mood and Anxiety Disorders Program, National Institute of Mental Health, NIH, Bethesda, MD, USA
Brain derived neurotrophic factor (BDNF) is required for neuronal plasticity, but the mechanism of its action and behavioral functions are not completely understood. In the hippocampus BDNF can be released from both pre- and post-synaptic cells, but neither the target, nor the source of BDNF involved in plasticity has been identified. Using Cre-loxP system, we show that the pre-synaptically and not post-synaptically secreted BDNF is required for neuronal plasticity in the hippocampal CA3-CA1. Deletion of BDNF from CA1 did not prevent mice from learning spatial task, but delayed relearning. More widespread deletion of BDNF increased fear-related behaviors.

BDNF bridges the gap between NMDA receptor blockade and dopamine hyperactivity.
Pierre Sokoloff, Unité de Neurobiologie et Pharmacologie Moléculaire, INSERM, Paris, France
P Sokoloff, L Leriche, J Diaz.
Schizophrenia is thought to involve hyperactivity of the neurotransmitter dopamine: symptoms are corrected by dopamine receptor blockade and exacerbated by dopamine-releasing agents. However, sustained blockade of glutamate neurotransmission by antagonists at the N-methyl-D-aspartate (NMDA) receptor subtype, such as phencyclidine, produces a range of symptoms remarkably similar to schizophrenia and drugs facilitating this neurotransmission improve symptoms of the disease. The relationships at the molecular level between dopaminergic and glutamatergic systems in schizophrenia are not understood. Here we show that chronic NMDA receptor blockade produces in mice behavioral disturbances related to schizophrenia, including spontaneous hyperactivity, hypersensitivity to psychostimulants and social interaction deficits, as well as neurochemical abnormalities found in patients with schizophrenia, i.e. upregulations of brain-derived neurotrophic factor (BDNF) and dopamine D3 receptor (DrD3), and downregulation of reelin, a factor involved in cortical development. All these abnormalities are corrected by administration of antipsychotic DrD2/DrD3 blockers, such as clozapine, or selective DrD3 blockers, and in DrD3-/- mice. Moreover, chronic antipsychotic treatment normalizes BDNF expression and BDNF hypomorphs are not sensitive to NMDA receptor blockade. Since BDNF is produced by glutamatergic neurons and controls Drd3 expression, this factor may causally relate glutamate to dopamine dysfunctions in schizophrenia and represent a previously unrecognized target of antipsychotic drugs. Unité de Neurobiologie et Pharmacologie Moléculaire, INSERM U 573, Paris, France.

The role of neurotrophins in the CNS drug action.
Eero Castrén, Neuroscience Center, University of Helsinki, Finland
Neurotrophins are regulated by neuronal activity and they are key regulators of activity-dependent synaptic stability and plasticity in the CNS. Resent data suggest that neurotrophins may play an essential role in the mechanism of CNS drug action. Antidepressant drugs increase the production and release of BDNF in prefrontal cortex and hippocampus and the activation of BDNF receptor trkB by increase BDNF release

appears to be critical for the behavioral actions of antidepressants. Opioids induce the release of NT-4 in the brain stem area and NT-4 contributes to the analgesic action of morphine. Furthermore, certain classes of neuroprotective drugs increase the production or release of neurotrophins and this effect may play a role in their neuroprotective effect. These data suggest that neurotrophin release induced by neuronal activity or CNS drugs may be essential for the selection, maintenance and restoration of functional neuronal networks.

Invited Talks – Outstanding Young Investigator Awardees: Friday, November 7th, 1:30 p.m.

Functional variation in vasopressin 1a receptor gene structure within and between vole species predicts behavior.

Elizabeth Hammock, Center for Behavioral Neuroscience, Emory University, Atlanta, GA, USA
E Hammock1,2, M Lim1,2, H Nair1,2, L Young1,2,3.

Brain vasopressin 1a receptors (V1aR) regulate social behavior in a species- specific manner. The neuroanatomical distribution of V1aR is highly variable across species. A sequence comparison of the V1aR gene of monogamous prairie voles and polygamous montane voles implicates a microsatellite expansion in the 5' region of the prairie vole V1aR gene. The length of this prairie-vole specific microsatellite expansion is variable among individual prairie voles. In cell culture, the prairie vole V1aR microsatellite acts as a repressor of luciferase reporter expression in A7r5 cells (t-test, $P<0.05$), suggesting that it could act the same way in the brain to regulate V1aR expression. Species-specific lengths of microsatellite exhibit different regulatory abilities (t-test, $p<0.05$), suggesting that length variations could also affect gene expression. To assess an in vivo role for the microsatellite, 20 male prairie voles were put through several behavioral assays (elevated plus maze, open field test, resident-intruder, juvenile affiliation, paternal care, partner preference), their brains were assayed for V1aR autoradiography and they were genotyped for the length of their microsatellite alleles. Preliminary analysis indicates multiple relationships between genotype and V1aR binding, genotype and behavior, and V1aR binding and behavior. Because microsatellites are known to rapidly expand and contract, these findings suggest an exciting mechanism for the rapid evolution of complex behaviors, as well as a molecular mechanism which could explain some individual differences in behavior.

1Ctr Behav Neurosci, Emory Univ, Atlanta, GA, USA, 2Yerkes National Primate Center, 3Dept Psych & Behav Sci, Emory Univ, Atlanta, GA, USA. NSF STC IBN-9876754, NIH MH67397 to EH, MH56897 & MH64692 to LY, Yerkes Center Grant RR00165.

Novelty seeking and dopamine receptor polymorphisms in adolescence.

Noa Heiman, Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA
N Heiman1, M Larsson2, MC Stallings1, SE Young1, A Smolen1, JK Hewitt1.

The importance of genetic contributions to personality traits is well established, as indexed by moderate heritability estimates found in twin studies. In addition, several studies have reported associations for a particular variant of the dopamine D4 receptor gene (known as the 'long repeat allele') with the personality trait of novelty seeking. The DRD4 gene has a variable number of tandem repeats (VNTR) in its third exon, which have been shown to affect the function of the D4 receptor efficiency in vitro. However, replication studies have shown mixed results. The aim of our study was to investigate whether such an association replicates in a large adolescent sample. Our sample consisted of 2185 adolescents between the ages of 11 and 18. Adolescents were drawn from the Colorado Twin Registry, the Colorado Adolescent Substance Abuse family study and the Colorado Adoption Project. Novelty seeking was measured using the Tridimensional Personality Questionnaire (TPQ) in adolescents aged 16 and older. For children under age 16 the Junior Temperament and Character Inventory (J-TCI) was used. We found no evidence for an association between novelty seeking and the DRD4 VNTR. Analysis of variance yielded non-significant results both when defining the predisposing allele as having seven or more repeats, and when comparing the presence or absence of seven repeats only. Including covariates such as age, gender, and ethnicity yielded non-significant results as well. A sub-sample composed of one sibling randomly selected from each family yielded a significant association but in the opposite direction than expected. Allele frequencies for both definitions of the predisposing allele were slightly higher in a clinical sample, selected for substance use and conduct disorder, than in the community sample. Additional analyses will investigate potential associations

between novelty seeking and other polymorphisms in the dopamine system, as well as potential epistatic effects between candidate loci. 1Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA, 2Center for Developmental Research, Orebro University, Sweden.

Novelty-seeking behaviors and alcohol preference in mice lacking alpha1G T-type Ca2+ channels.
Daesoo Kim, National CRI Centre for Calcium and Learning, Korea Institute of Science and Technology, Seoul, Korea
D Kim, S Choi, J Lee, S Lee, M Sun, J Park, H Sung, H-S Shin.
Novelty/sensation seeking is the tendency to pursue novel and stimulating experiences, which is often associated with risk-taking behaviors, drug abuse or crimes in humans. Mechanisms underlying this behavior are poorly understood. Mice lacking alpha1G T-type Ca2+ channels showed an increased exploratory behavior in novel environments or to novel objects when compared with wildtype. Mutants showed a shorter latency to the first approach to novel objects, more active engagements with the objects, such as pushing and toying, during the exploration. The mutant showed normal performance in novelty-discrimination tests, and had an intact capacity for the acquisition of contextual and cued memory in the fear conditioning assays. In contrast to reports on attention-deficit hyperactivity (ADHD) or schizophrenia models, the hyper-response of the mutant was transient and disappeared rapidly as the mouse was acclimated to the novel situations. Those behaviors of the mutant were suppressed to the level of wild type by treatment with a well-known mood stabilizer, lithium chloride. Similar to that has been examined in novelty-seeking personality in human, preference to alcohol was also altered in the mutants. In the two-bottle choice test where water and alcohol is supplied with separated bottles, the mutant showed a significantly higher alcohol preference (65 %) than wild type (35 %), as measured by a percent amount of alcohol consumption in daily total drinking. The present results indicate that alpha1G T-type calcium channels play a role in the control of affective reactions to novelty and in the gain of alcohol preference. These findings shed light on the possible mechanism for affective disorders and drug abuse which are often associated with a novelty-seeking personality. Korea Institute of Science and Technology, Seoul, Korea. Supported by National CRI grants of Korea, Ministry of Science of Technology, Korea.

A glutamatergic basis for impaired ethanol-induced plasticity in Homer2 null mutant mice.
Karen Szumlinski, Physiology and Neuroscience, Medical Univ of South Carolina,Charleston, SC, USA
KK Szumlinski1, CT Smothers1, NP Champtiaux1, S Toda1, LD Middaugh1,2, PF Worley3, PW Kalivas1.
Constitutive forms of Homer proteins are synaptic scaffolding proteins that regulate multiple aspects of glutamate receptor signaling. Given the importance of glutamate transmission in the development of the acute and long-term behavioural effects of ethanol, a series of experiments were conducted in which wild-type (WT) mice and mice with a homozygous deletion of the Homer2 gene (Homer2 KO) were compared on measures related to the rewarding and motor-activating effects of this drug. Homer2 KO mice exhibited increased ethanol aversion, increased ethanol-induced sedation and a lack of tolerance of ethanol-induced locomotor-inhibition following repeated administration. Although Homer2 deletion did not alter basal extracellular levels of dopamine in the ventral striatum, gene deletion produced an approximately 50% reduction in ventral striatal extracellular levels of glutamate. An acute injection of ethanol (3 g/kg) reduced extracellular levels of both dopamine and glutamate in both genotypes. However, the impaired behavioural tolerance noted for Homer2 KO mice was associated with a lack of glutamate and dopamine sensitization in the ventral striatum following repeated ethanol administration. The genotypic differences in ethanol-induced behavioural plasticity may be related to genotypic differences in mesocorticolimbic mGluR1a receptor function as Homer2 deletion produced a 25% reduction in ventral striatal mGluR1a protein, a blunted capacity of intra-ventral striatal group1 mGluR stimulation to increase motor activity and extracellular glutamate. Although Homer2 deletion produced no observable effects upon ventral striatal NMDA receptor subunit expression, a reduction in whole-cell current through hippocampal NMDA receptors and an increased locomotor response to both non-competitive and competitive NMDA receptor antagonists were observed in Homer2 KO mice. Collectively, these data indicate that Homer2-regulation of mesocorticolimbic mGluR1a and NMDA function is involved in the determination of acute ethanol sensitivity and ethanol-induced neural plasticity, both of which contribute to addiction vulnerability. 1Department of Physiology and

Neuroscience1 and 2Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston SC, USA; 3Department of Neurosciences, The Johns Hopkins University School of Medicine. Supported, in part, by NIDA grants DA-03906 (PWK), DA-11742 (PFW), NIAAA grants AA09986, AA00238 (JJW), P50-AA10761 (LDM), NIMH grant MH-40817 (PWK) and a postdoctoral fellowship to KKS (CIHR).

Symposium Session IV: Friday, November 7th, 4:00 p.m.

Symposium Abstract:
Genotype-environment interactions in behavioral phenotyping: So what are we supposed to do about them?
Chair & Organizer: Neri Kafkafi, Maryland Psychiatric Research Center, University of Maryland, Baltimore, Maryland, USA
To elucidate pathways from specific genes to complex behaviors, assays of mouse behavior need to be valid, reliable and replicable across laboratories. While better standardization of housing and test parameters remains desirable, recent studies suggest that it is not likely to eliminate the interaction effect. The symposium will focus on several complementary approaches to this problem.

(In)stability of brain size and behavior over decades in different laboratories.
Douglas Wahlsten, Dept. of Psychology, University of Alberta, Edmonton, Alberta, Canada
D Wahlsten, T Mosher.
Recent studies of identical behavioral tests of genetically identical mice run simultaneously in more than one lab have demonstrated that relatively subtle variations in the lab environment can have strain-specific consequences. It is also informative to compare measures of standard inbred strains obtained in different labs many years apart, provided the measured phenotypes are essentially the same. Data for brain weight and open field activity from studies reported more than 20 years apart reveal instances of remarkably robust strain differences as well as substantial shifts in strain rank orders. Relevance of these findings for the understanding of genotype x environment interaction and the long-term replicability of experiments in neurobehavioral genetics will be discussed. Dept. of Psychology, University of Alberta, Edmonton, Alberta, Canada.

Identification of laboratory environment factors influencing a behavioral trait via computational analysis of a large data archive.
Jeffery S. Mogil, Dept. of Psychology, McGill University, Montreal, Quebec, Canada
Given the renewed interest in the effects of environmental factors on behavior genetic experiments, it behooves us to identify as many of these factors as possible. In general, such factors are investigated one at a time, without consideration of their importance relative to other factors. By analyzing an archive of baseline measurements of thermal nociceptive sensitivity over an 8-year period, we identified and ranked the relative influence of organismic, husbandry and test-specific environmental influences on variability in this trait.

Designing better measures of behavior using a multi-lab database of raw data.
Neri Kafkafi, Maryland Psychiatric Research Center, University of Maryland, Baltimore, Maryland, USA
The ever-improving technologies of automatic tracking, data storage and interactive programming promote a new approach to an old question: what are the proper variables one should use for measuring complex behavior? It is now possible to maintain databases of raw behavioral data gathered from many genotypes, treatment and laboratories, and use them for “in silico” spotting and even designing measures that are more discriminative and more replicable. Examples and results from a database of open field behavior of 8 mouse genotypes across 3 laboratories will be discussed.

Is this interaction good or bad? Mixed Model statistical analysis of multi-lab results.
Yoav Benjamini, Dept. of Statistics and Operation Research, Tel Aviv University, Tel Aviv, Israel

A statistical approach using the Linear Mixed Model of two way ANOVA will be described, which recognizes that genotype x laboratory interaction is an inevitable fact of life, and uses it as the yardstick for estimating the genotype effect. The method sets a higher benchmark for showing a genotype effect, but results garnered from 3 laboratories demonstrate that genotype effects in many measures still remain significant. The approach allows for single-lab studies when using tests and measures for which the interaction was estimated in a previous multi-lab study. Implications for QTL and screening studies will be discussed.

Poster Session - Thursday, November , 6th, 4:00 p.m.

IBANGS – 01 Paper Session – Oral Presentation
Overexpression of NTRK3 increases anxiety-like behavior and alters monoaminergic circuits in mice.
M Dierssen1, M Gratacòs1, I Sahún1, M Martín2, X Gallego1, A Amador-Arjona1, MM de Lagrán1, P Murtra2, MA Pujana1, R Maldonado2, C Fillat1, X Estivill1,3
The neurotrophin type 3 receptor(NTRK3) maps to a human chromosome 15 region postulated to be involved in anxiety disorders, and is the only neurotrophin receptor expressed in the locus coeruleus (LC). This genomic region is duplicated in panic patients, and thus a gene dosage effect could be proposed. A possible mechanism would be that increased dosage of NTRK3 would alter synaptic plasticity in the LC by changing local trophic support, and would produce abnormal function of catecholaminergic neurotransmitter systems leading to panic disorder. In order to evaluate this hypothesis, we have developed several lines of transgenic mice that overexpress NTRK3, under the control of the PDGFB promoter. Stereological analysis demonstrates that NTRK3 overexpression causes an increase in the volume of LC and in the number and density of tyrosine hydroxilase (TH) positive neurons in this region. TgNTRK3 mice showed an increased anxiety-like behavior in different tests and an enhancement of panic reaction in the mouse defense test battery (MDTB). Response to the panicogenic agent yohimbine, was paradoxical in TgNTRK3 brains, suggesting 2 adrenoreceptors deregulation. These results raise the possibility that overexpression of NTRK3 would be determinant for the development of panic disorder through the regulation of neural plasticity in specific monoaminergic circuits involved in the pathogenesis of this disorder and suggest a new pathogenetic mechanism via 2 adrenoreceptors deregulation. 1Program in Genes and Disease, Genomic Regulation Center-CRG, Barcelona Biomedical Research Park, E-08003 Barcelona, Catalonia, Spain, 2Unit of Neuropharmacology, Pompeu Fabra University, Barcelona Biomedical Research Park, E-08003 Barcelona, Catalonia, Spain and 3Unit of Genetics, Pompeu Fabra University, Barcelona Biomedical Research Park, E-08003 Barcelona, Spain. 2This work was supported by Spanish Ministry of Science (SAF2001-1231, SAF2002-00799) and Fundació Marató TV3. MML is recipient of a MICYT fellowship.

IBANGS – 02 Paper Session – Oral Presentation
Impairment of APP transgenic mice in spatial and associative learning.
C Janus
Deposition of ß-amyloid peptide in the brain is a major pathological feature of Alzheimer's Disease. Transgenic mice (TgCRND8) encoding a double mutated allele of human APP genes (Swedish; KM670/671NL+Indiana; V717F) develop extracellular amyloid deposits in the hippocampus and forebrain and are impaired in spatial reference and working memory from 12 weeks of age onwards. In this study, 35-week old TgCRND8 mice with abundant amyloid brain pathology and non-transgenic (non-Tg) littermates were given a longitudinally administered battery of cognitive tests including: (a) a visible platform version of Morris water maze (MWM) test, (b) a reference memory MWM test, and (c) conditioned taste aversion (CTA) test (i.e. learning the association between novel taste and induced nausea). The results demonstrated that TgCRND8 mice exhibited greater variability of responses as compared to non-Tg littermates in all tests. In addition, they showed a significant impairment in escaping to cued and hidden escape platforms, as well as impairment in the association between novel taste of saccharine and LiCl-induced (i.p. injection) nausea. There was no significant association between performance in all 3 tests in non-Tg mice. In contrast, in TgCRND8 mice impaired performance in a cued version of MWM was significantly positively correlated with their impaired learning during CTA test. The scores of the two types of associative learning were not correlated with levels of amyloid beta in the brain. However, the impaired performance in the reference

memory MWM test was significantly positively correlated with both soluble and insoluble (formic acid extracted) forms of amyloid beta peptide. CRND, Univ. of Toronto, Toronto, Canada.

IBANGS – 03 Paper Session – Oral Presentation
Identification and quantitation of neurons expressing NR1 transgenes that modifies behavior, from HSV-1vectors injected into the hippocampus.
V Cheli1,2, M Adrover1,3, C Blanco1, A Cornea2, G Sánchez1, N Colettis1, M Snitcofsky1, E Martín1, A Epstein3, D Jerusalinsky1
We have shown that the expression of NR1 and GFP transgenes from HSV-1 derived vectors injected into the dorsal hippocampus of adult Wistar rats, mainly happened into neurons, in a discrete region. The NR1 expression was reduced in primary cultures of neurons, and in the hippocampus of rats injected with a NR1 antisense expressing vector. They suffered an impairment in performance of both, an open field test for habituation to a new environment, and an inhibitory avoidance to a foot-shock; while rats injected with the vector expressing NR1 did not show significant differences compared to naive animals. These results - together with evidences previously reported- suggested that the NMDA receptor in the dorsal hippocampus participates in mechanisms leading to habituation, as well as in acquisition and/or consolidation of the inhibitory avoidance, since both tasks suffered serious impairements even after slight changes in the availability of the NR1 subunit. However we knew neither the area nor the identity of cells infected, and presumably responsible for those changes. The animals were injected with vectors expressing both NR1 sequences and GFP; brain slices were immunostained to identify neurons and glia, and the transgenes. The cells were identified and quantitated under confocal microscopy, using an ad hoc software. Our data showed that most of the infected cells are pyramidal or granule neurons in a restricted area under the injection, and that only a few astrocytes expressed GFP. The quantitation suggested that only about 8-10 % of the neurons in that region were affected. Hence, it would mean that a single gene transfer in just a few neurons -and a slight modification in the protein-, is enough to produce those significant alterations in learning and memory. 1IBC&N, Sch. Med., and Dept. Anat., Sch Vet., Univ. of Buenos Aires, Argentina, ONPRC-OHSU, Oregon, USA, 3Ctr. of Mol. & Cell. Genetics, Univ. Claude Bernard, Lyon , France. Supported by Guggenheim Foundation, Fogarty Tech. Assist. Grant (USA); CNRS/CONICET (France-Argentine), ANPCYT and Univ. Bs. As. (Argentine).

IBANGS – 04 Paper Session – Oral Presentation
Altered responses to ethanol in mice lacking functional N-type calcium channels.
PM Newton1, Orr CJ1, Shin HS2 Messing RO1
N-type calcium channels are important for neurotransmitter release and are the target of many neuromodulators, including opioids and adenosine. Previous work in our laboratory has shown that acute ethanol treatment inhibits N-type calcium channel function, and that chronic ethanol vapor inhalation treatment increases the density of N-type calcium channels in the frontal cortex and hippocampus of mice. These data suggest that N-type calcium channels may be a molecular target for acute alcohol intoxication, and may also form part of the neuroadaptive changes that occur in response to chronic alcohol exposure. In order to test these hypotheses, we studied alcohol responses in mice lacking the alpha-1B subunit of N-type calcium channels. F1 hybrid (129SvJ x C57/BL6) male alpha-1B knockout mice showed a reduced preference for ethanol, both in two bottle choice and place preference assays. They showed a dramatically decreased sensitivity to ethanol in the loss of righting reflex assay, but a slightly increased sensitivity to ethanol-induced ataxia on the accelerating rotarod. Suprisingly, handling induced convulsion scores following chronic exposure to ethanol vapor were increased in the knockouts. Clearance of ethanol from the blood did not differ between genotypes. These data suggest that N-type calcium channels mediate some of the hypnotic and rewarding effects of ethanol. Upregulation of N-type calcium channels after chronic ethanol exposure may limit manifestations of alcohol dependence. 1Ernest Gallo Research Center, Department of Neurology, University of California San Francisco, Emeryville, CA, 94608 USA. 2National Creative Research Initiatives Center for Calcium and Learning, Korea Institute of Science and Technology, Seoul 136-791, Korea. This work was supported by funds provided by the National Institutes of Health, grant number AA08117.

IBANGS – 05 Paper Session – Oral Presentation

Gene expression profiles of GABAA α1 subunit-deficient mice: comparison of two knock-out models.

I Ponomarev1, G Schafer1, YA Blednov1, GE Homanics2, RA Harris1

The α1 subunit of GABAA receptors is a constituent of the major GABAA receptor subtype in the murine brain. Mice lacking this subunit demonstrate a number of physiological and behavioral alterations, including a marked ethanol-induced locomotor stimulation (Blednov et al. JPET 2003 Jan., JPET 2003 Mar.; Kralic et al., JPET 2003). The objective of the present study was to determine whether deletion of this gene in mutant mice produced changes in expression of other genes. Another objective was to compare gene expression profiles of two independently created GABAA α1 KO models. We used cDNA microarrays to examine expression profiles of GABAA α1 knock-out (KO) and wild type (WT) animals. Total RNA was isolated from cerebellum or midbrain region of KO and WT littermates. Genisphere ® 3DNA technology kit was utilized for reverse transcription, labeling and hybridization of the tissue cDNA on a glass slide containing ~16000 elements. Relative expression for each gene was calculated and averaged across 3-9 mice per genotype. Based on a two-sample t-test at $p<0.01$, about 1% of all detected genes were differentially expressed in two genotypes. Among the most substantial alterations in mutant mice was differential expression of midkine, a growth factor found in senile plaques of Alzheimer's patients. About 6% of all significantly detected genes were similarly regulated for the two KO models. We hypothesize that alteration in expression of some genes, such as GAP-43 and ARPP-21 may influence ethanol-related behaviors in KO mice. 1Waggoner Center, University of Texas, Austin, Texas, USA, 2University of Pittsburgh, Pittsburgh, Pennsylvania, USA. Supported by the NIAAA INIA program (grants: AA13520, AA13518).

IBANGS – 06 Paper Session – Oral Presentation

Glutamate receptors and long-term memory in C. elegans.

C Rankin, J Rose, S Steidl

Long-term memory in C. elegans depends on glr-1, a homologue of mammalian non-NMDA glutamate receptors, expressed on the interneurons of a mechanosensory circuit. Both mutations in glr-1 and an AMPA receptor antagonist blocked long-term memory. We used a genetic marker to visualize glr-1 expression in the interneurons of trained and untrained worms and a marker for vesicles to look for changes in the tap sensory neurons. Trained animals had less glr-1 expression than untrained animals; there was no difference in expression of the vesicle marker. Thus, long-term memory in C. elegans is dependent on glr-1 and involves post-synaptic but not pre-synaptic changes in gene expression. avr-14 encodes a a-type subunit of a glutamate-gated chloride channel (GluCls) expressed on the glutamatergic mechanosensory neurons of the tap-withdrawal response that synapse onto the command interneurons. The mutation selectively effects short-term habituation for shorter interstimulus intervals (ISIs; 10s and 30s) while not effecting habituation for long ISIs (45s and 60s). These results provide support for the hypothesis that in C. elegans there are multiple ISI-dependant short-term memory systems. avr-14 worms show long-term memory for habituation training comparable to wild-type controls when given distributed training and testing with a 60s ISI. avr-14 worms, unlike wild-type controls, also show long-term memory when trained and tested with a 10s ISI. Furthermore, long-term memory for this training protocol is protein synthesis dependant, as administering heat shock in between blocks of training blocks the formation of long-term memory. This suggests that in wild-type worms the presence of avr-14 blocks the conversion from short-term to long-term memory following training with short ISIs. Dept of Psychology & Brain Research Centre, Univ. of British Columbia, Vancouver, British Columbia, Canada. Research supported by NSERC, CIHR and BCMCFH-HELP.

IBANGS – 07

Genetic differences in serial reversal learning.

CJ Heyser

The behavioral differences described among genetically distinct strains of mice can be highly influenced, even dependent, on the methodology employed. For example, we have previously reported differences in active avoidance learning among a variety of mouse strains and, more importantly, that these differences can be accentuated or eliminated by altering the parameters of the task. The current study was conducted to examine whether similar results would be obtained using an appetitive (food motivated) task. Serial reversal learning was examined in Balb/cByJ, DBA/2J, C57BL/6J, and C57BL/6xSJL F1-hybrid mice using a discriminated operant conditioning task. All animals were trained to nosepoke for food on a continuous

reinforcement schedule (FR-1). Mice in Condition-I remained on FR-1, whereas mice in Condition-II had their response requirement increased to FR-10. The significance of the holes was reversed when each animal achieved a discrimination index greater than 80%. In Condition-III, the response requirement was increased to FR-3 and reversal occurred when the animal exhibited a discrimination index greater than 80% for 3 consecutive days. These procedures were repeated until 5 reversals were completed. Balb, C57BL, and C57BL/6xSJL mice acquired the initial phase equivalently, whereas DBA mice required significantly more training to reach reversal criterion when response requirements were low (FR-1 and FR-3). However, all mice reached criterion for the first reversal in the same number of training sessions when the response requirement was higher (FR-10). Differences among the strains were observed during the serial reversal phase and these interacted with the parameters of the task. Therefore, acquisition of a discriminated operant task and flexibility in learning, as assessed by a serial reversal procedure, is influenced by the parameters of the task and the genetic background of the organism. Dept. of Psychology, Franklin & Marshall College, Lancaster, PA, USA.

IBANGS – 08
Genetic influences on mouse models of novelty seeking.
CL Kliethermes, JC Crabbe
Novelty seeking is a normal personality trait, and increased novelty seeking has been correlated with the expression of alcohol and drug abuse. Multiple mouse models of novelty seeking exist, each of which could be influenced to varying degrees by the genotype of the mouse. These models are based on either the extent to which novel stimuli are explored, or the relative preference for novel over familiar stimuli. We tested eight inbred and one F1 hybrid strains of mice in six mouse models of novelty seeking in order to obtain broad-sense heritability estimates for each model. The models tested included the locomotor response to novelty, preference for a novel environment, head dipping on a hole board, preference for objects, preference for a novel object, and spontaneous alternation. Strain differences were observed for all models, although the extent of the differences varied depending on the particular model. The locomotor response to novelty and head dipping on a hole board appeared to be highly heritable ($h2 = 0.81$ and 0.69, respectively), while preference for a novel object resulted in a lesser estimate of 0.21. Locomotor activity in all models was highly genetically correlated with the locomotor response to novelty, but fewer correlations were found among the other variables. These results support the notion that novelty seeking is a complex trait influenced by genetic factors, and suggest caution in extending the results obtained from any single model of novelty seeking. Portland Alcohol Research Center, Behavioral Neuroscience, OHSU, Portland, OR, USA, Dept. of Veterans Affairs Medical Center, Portland, OR, USA. This research was supported by AA10760, the Department of Veterans Affairs, and 5T32DA07262.

IBANGS – 09
Behavioral assessment of visual discrimination in seven strains of mice.
AA Wong, RE Brown
Based on the procedure of Prusky et al. (2000, Vision Research, 40, 2201-2209), we used a computer-based, two-alternative swim task to evaluate visual discrimination, pattern discrimination and visual acuity in seven strains of mice (BALB/cByJ, C3H/HeSnJ, C57BL/6J, DBA/2J, FVB/NJ, MOLF/Ei and SJL/J). Each mouse was tested for 8 trials/day for 8 days on each of the three tests. There was a significant strain difference in visual ability in all three tests. Mice with normal vision (C57BL/6J and DBA/2J) performed very well in these tasks. Mice with poor vision (BALB/cByJ) took longer to learn the tasks than mice with normal vision and mice with retinal degeneration (C3H/HeSnJ, FVB/NJ, MOLF/Ei and SJL/J) performed only at chance levels. Because this task provides a quantitative measurement of visual ability and is sensitive enough to detect small differences between strains, we suggest that this task should be used as a preliminary investigation of visual ability before mice are tested on visio-spatial tasks. Psychology Department, Dalhousie University, Halifax, N.S. Canada B3H 4J1. Supported by grants from NSERC of Canada and the March of Dimes.

IBANGS – 10
Comparison of C57/BL6, DBA/2J, FVB/NJ on social behaviors relevant to autism.
JJ Nadler1, A Perez2, NB Young2, RP Barbaro1, SS Moy2, TR Magnuson1, JN Crawley3

Autism is a neurodevelopmental disorder characterized by social deficits, abnormalities in communication and stereotypic ritualized behaviors. The severity of these behaviors varies widely from patient to patient and can even be found to some extent in unaffected family members. In order to investigate the genetics of autistic behaviors, we are examining multiple inbred strains of mice for social and cognitive function describing a range of phenotypes from normal to autism-like. The specific functions tested are social interaction with a social preference test, cognitive flexibility by T-maze and Morris water maze, and social communication through monitoring of ultrasonic vocalization of pups. 1Department of Genetics, 2Neurodevelopmental Disorders Research Center, University of North Carolina, Chapel Hill, NC, USA; 3Laboratory of Behavioral Neuroscience, IRP, National Institute of Health, Bethesda, MD, USA.

IBANGS – 11

Characterization of a procedure to assess ethanol-induced ataxia.

HM Kamens1, TJ Phillips1, D Wahlsten2, JC Crabbe1

Ataxia, or impairment of motor coordination, presents itself as one of the earliest effects of alcohol ingestion in humans and animal models. Many procedures to assess this in rodents are currently in use, but evidence from our lab suggests that these tasks measure different components of this trait. We have characterized the parallel rod floor apparatus to quantify ethanol-induced ataxia. First, genetically heterogeneous mice were used to evaluate the influence of rod diameter and inter-rod distance on ethanol-induced ataxia for the purpose of selecting parameters that optimize ataxia measurements. We then used the DBA/2J and C57BL/6J inbred strains of mice to examine the effect of serially testing mice on multiple floor types at a single ethanol dose. Finally, we tested eight inbred strains of mice on 4 floor types to examine strain sensitivity patterns to 2-g/kg ethanol, and determine the best testing parameters to maximize strain effect size. Repeated-measures ANOVAs revealed differences in the amount of ataxia seen on the floor types, and identified strain differences in amount of ataxia after ethanol (p's<0.05). When data from strain 129S1/SvImJ were removed from the analyses, significant strain differences were found for only one floor type. The greatest strain effect size was observed during the first ten minutes of testing after 2-g/kg ethanol. These findings suggest that the parallel rod floor task provides a useful task for examining ethanol-induced ataxia in mice, but that specific characteristics of the floor are important. 1Portland Alcohol Research Center, Behavioral Neuroscience, Oregon Health & Science University and VA Medical Center, Portland, Oregon, USA, 2Psychology and Centre for Neuroscience, University of Alberta, Edmonton, Alberta, Canada. Supported by: Department of Veterans Affairs and NIH Grants P50 AA10760, R01 AA12714, and T32 AA07468.

IBANGS – 12

Phenotyping the rat: Efficiency of strain identification with a simple operant test.

GM Harrington

Diagnosis consists of obtaining a battery of test results, comparing the results with normed data, and assigning the subject to a group on the basis of the test profile. It was the intent of the author's rat phenotyping program to model a behavioral diagnostic system with genetic controls. The criterion for selection of the species, of the strains, and of the tests was frequency of representation in research publications. (This differs somewhat from the more recent Mouse Phenome Project objectives and criteria.) Maze tests showed significant strain by test item (maze pattern) interactions. The number of genetic factors for this effect was greater than 6 but no greater than 50. Recognition that a large part of the genome is regulatory and emerging evidence of the importance of synchronization and ultradian rhythms suggest extending examination of physical maze behavior to a temporal maze (operant conditioning). Time samples were taken from the phenotyping operant test raw data for 407 animals from 12 of the Har strains: ACI, A990, A35322, F344, INR,IR, MNR, MNRA, MR, TS1, TS3, and WAG. For a century, behavioral studies have relied on data reduction methods to render data manageable through creation of more limited sets of "as if" variables or constructs, e.g., "factors", "QTL's". The reduced variable number typically is more than an order of magnitude smaller than the number of variables comprising the biological substrate. Modern computing makes it possible to manage higher dimensional analysis at an order closer to the number of genes actually affecting the behavior. Maximum likelihood estimation data reduction yielded 22 variates with eigenvalues greater than one, 35 variates for high efficiency of strain identification, and 105-110 variates to

meet Fisher's standard that a genetic model should predict the correlation matrix. Department of Psychology, University of Northern Iowa, Cedar Falls, Iowa, USA.

IBANGS – 13

Short-term memory impairment is related to hippocampal c-Fos expression in an animal model of Fetal Alcohol Syndrome.

K Clements1, T Girard2, C Ellard1, P Wainwright2

Previous work in our laboratory has shown that exposure to ethanol during the brain growth spurt impairs short-term memory (STM) in rats assessed using a spatial delayed matching-to-place (DMP) version of the Morris water maze. The main objectives of this study were to ascertain whether the STM impairment in ethanol-exposed (EE) rats could be related to 1) length of encoding time and 2) hippocampal c-Fos expression. Using an artificial rearing model, rats were fed 6.5g/Kg/day of ethanol from postnatal days 6 -9, with controls fed an isocaloric amount of maltose dextrin. As adults the rats were trained on one of two tasks, either the DMP task, which consisted of an initial search trial and subsequent recall trials, or a random platform version which incorporated the same performance requirements as the DMP task. As expected EE rats took longer to learn the DMP task but attained the level of performance of controls by the end of training. EE rats also had longer search trials during training due to their use of a different search strategy involving thigmotaxis. Increasing the delay between the search and recall trials impaired performance in EE but not control rats. However, varying the length of the encoding time did not affect their performance. Brain c-Fos expression was increased in both visual and prefrontal cortex in rats trained on the DMP compared to the random task. In the DMP-trained animals, brain c-Fos expression in EE rats was lower in hippocampus, but not other brain areas. Hippocampal c-Fos expression also correlated significantly with the distance swum on the search trial. These results indicate that 1) the ability of EE rats to benefit from manipulation of encoding time is limited and 2) the STM impairment seen in EE rats is related to a decrease in c-Fos expression in the hippocampus. 1Department of Psychology and 2Department of Health Studies and Gerontology, University of Waterloo, Ontario, Canada. This work was supported by a Natural Sciences and Engineering Research Council of Canada grant to P. Wainwright.

IBANGS – 14

Assessment of ethanol consumption in dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) knockout mice in a limited access paradigm.

FS Hall1, CP Mills1, I Sora2, GR Uhl1

Several lines of evidence suggest that monoaminergic systems, especially dopaminergic and serotoninergic systems, modulate ethanol consumption. Humans display significant differences in expression of the vesicular and plasma membrane monoamine transporters important for monoaminergic functions, including the vesicular monoamine transporter (VMAT2, SLC18A2) and dopamine transporter (DAT; SLC6A3). We have previously shown that ethanol consumption was affected by these gene knockouts using a two-bottle home cage testing procedure (Hall et al, Neuropsychopharmacology 2003). Here we now report a further assessment in these mice of ethanol consumption using a limited access paradigm. In this paradigm mice were placed each day for 15 minutes in a testing cage, identical to the home cage, containing two fluid sources, water and ethanol. Ethanol concentrations were assessed in order of ascending concentration (2%, 4%, 8%, 16%, 32%) for 5 days each. VMAT2 gene knockout reduced ethanol consumption at higher ethanol concentrations while DAT gene knockout increased ethanol consumption at higher concentrations. There was no effect of either gene knockout on water consumption. These data provide further support a role for monoaminergic systems in modulation of ethanol consumption, and for monoaminergic genes in the determination of sensitivity to the rewarding effects of ethanol. 1Mol. Neurobiol. Br., NIDA/IRP, NIH/DHHS, Baltimore, MD, USA, 2Tohoku Univ. Sch. Med., Dept. Neurosci., Sendai, Japan. 1Supported by intramural funding from NIDA/NIH/DHHS.

IBANGS – 15

Evaluation of a simple model of ethanol drinking in C57BL/6J mice.

JS Rhodes, JC Crabbe

When using mice as a model organism to study the pharmacogenetics of alcoholism it is often necessary to develop paradigms where mice voluntarily drink alcohol. Although this sounds obvious, the problem is that

many genotypes of mice do not drink alcohol unless they are water restricted, or are exposed to a complicated sucrose fading procedure. The aim of this study is to identify the optimal parameters and evaluate the reliability of a very simple procedure, taking advantage of a genotype (C57BL/6J) that is known to drink large quantities of alcohol. The simple procedure is to switch the water bottle with a solution containing 20% ethanol (in tap water) for a limited period and monitor ethanol consumption and blood-ethanol concentration (BEC). Here we evaluate the effect of varying the the duration of ethanol exposure (2 or 4 hours), the time when water is switched to ethanol (starting at 0,1,2 or 3 hours after lights off), and the number of days the procedure is repeated (4 or 15). We found that mice drank to pharmacologically significant levels under all conditions, but the highest BECs occurred when the water-to-ethanol switch occurred 2 or more hours into the dark cycle, and for the longer durations of ethanol access. Consumption of ethanol was consistent across days but only when considering the sum consumed over the entire 2 or 4 hour periods not for 30 min or 1 hour increments. Mice tended to drink sporadically which may have contributed to the large variation in BEC at any given timepoint. We discuss limitations of the model relative to the two-bottle choice test, and the utility of C57BL/6J as a mouse model of high alcohol drinking. Portland Alcohol Research Center, Behavioral Neuroscience, OHSU, Portland, OR, USA, Dept. of Veterans Affairs Medical Center, Portland, OR, USA. Support Contributed By: AA10760, AA113519, DA07262, & the Dept. of Veterans Affairs.

IBANGS – 16

Characterization of mice selectively bred for high and low rapid tolerance to ethanol.

NR Rustay, JC Crabbe

Ethanol tolerance, an important characteristic for the diagnosis of alcoholism, is often defined as a decrease in response to ethanol after repeated exposures to the drug. In rodents, rapid tolerance to a second injection develops within 24 hours of an initial ethanol exposure. Using genetically heterogeneous mice (HS/Npt), we artificially selected mice for high and low rapid tolerance to the incoordinating effects of ethanol using the accelerating rotarod. Mice were trained on the accelerating rotarod (2.5 in dia. rod at 20 rpm/min), followed by two consecutive days of testing under the influence of ethanol. For all tests, the latency to fall from the rod was recorded as the index of performance. The “tolerance score” (Day2-Day1 latency to fall after ethanol) was used as the selection index. Significant divergence between the high (HRT) and low (LRT) lines was seen after 3 generations of artificial selection. Realized heritabilities were .25 and .06 for HRT and LRT mice, respectively after 4 generations. These lines were tested for rapid and chronic (5 day) tolerance to 4 doses of ethanol (2.25, 2.5, 2.75, and 3.0 g/kg) to examine the relationship between rapid and chronic tolerance. Results indicated that HRT mice developed greater chronic tolerance, while LRT mice developed no significant chronic tolerance across the 5 days of testing. These results suggest that rapid and chronic tolerance development may be mediated by similar mechanisms. Past research has suggested a role for the NMDA receptor system in the development of rapid tolerance to ethanol’s ataxic effects. HRT and LRT mice will be examined to see if artificial selection has affected NMDA receptor density and sensitivity to NMDA receptor drugs. Portland Alcohol Research Center, Behavioral Neuroscience, OHSU, Portland, OR, USA, Dept. of Veterans Affairs Medical Center, Portland, OR, USA. This work was supported by NIH grants AA12714, AA10760, AA13463, the N.L. Tartar Trust, and a grant from the Department of Veterans Affairs.

IBANGS – 17

Acquisition of Tolerance to the motor incoordinating effects of ethanol during a restricted access paradigm.

K Cronise, DA Finn, JC Crabbe

This lab demonstrated that a fluid restriction paradigm produced excessive alcohol consumption and intoxication. Alcohol consumption may be influenced by the acquisition of tolerance. This study assessed if tolerance develops to alcohol-induced motor incoordination during consumption in mice predisposed to high alcohol consumption. Female C57BL/6J mice were allowed 3 hours of fluid daily with free access to food for 28 days. On day 1, mice received 3 hours of water. On day 2, mice received 30 minutes ethanol access (5% w/v) followed by 2.5 hours water access. Ethanol access was repeated every 2nd day, for 14 pairings. The controls had access to water only. Alcohol consumption was ~ 2.5 g/kg and blood ethanol concentrations (BEC) were ~1.5 mg/ml. Separate groups were tested for tolerance on the fixed speed rotarod (RR) @ 6.5 & 10 RPM immediately after ethanol or water access on days 2, 4, 6, 8, 10, 12, 14 and 16. Latencies to fall

across the 8 days were averaged to derive a baseline performance score. On day 17, all groups were injected with 2 g/kg ethanol and tested on the RR. Test day performance was expressed as a percent change from the baseline performance. The ethanol-experienced mice showed enhanced or stable performance while the ethanol-na ve group was impaired. BEC's did not differ (~1.5 g/kg). The results suggest: 1) C57BL/6J mice self-administer sufficient ethanol to produce tolerance in this paradigm; and, 2) this paradigm may assess the role of tolerance acquisition in alcohol consumption. Portland Alcohol Research Center, Behavioral Neuroscience, OHSU, Portland, OR, USA, Dept. of Veterans Affairs Medical Center, Portland, OR, USA. Support by: AA13478, AA10760, AA07468, & the Dept. of Veterans Affairs.

IBANGS – 18

A single injection of estradiol valerate alters ethanol- and saline-induced locomotion in selectively bred FAST and SLOW mice.

PJ Meyer1,2, M O'Connor1, TJ Phillips1,2,3

A single injection of the steroid estradiol valerate (EV) has been shown to cause long-term alterations of ethanol-induced locomotion as well as ethanol drinking patterns. This experiment examined the effect of EV on ethanol's locomotor effects in mice selectivity bred for increased (FAST mice), or decreased (SLOW mice) activity after an ethanol injection (2 g/kg). Female mice (5 weeks old) from each of two replicates of FAST (FAST-1 and FAST-2) and SLOW (SLOW-1 and SLOW-2) mice were injected subcutaneously with 100 mg/kg EV or sesame oil vehicle. Four weeks later, these mice were injected with either 2 g/kg ethanol or saline. In both replicates of SLOW mice, EV treatment potentiated ethanol's locomotor depressant effects, while ethanol's stimulant effect in FAST-1 mice was blocked. However, EV-treated mice, regardless of genotype, displayed less activity after a saline injection, compared to vehicle treated mice. While these findings suggest that EV treatment alters ethanol's locomotor effects, its effects were inconsistent in that it blocked ethanol stimulation in only one replicate line, and were non-specific in that EV treatment also reduced saline-induced activity. 1Department of Behavioral Neuroscience, Oregon Health and Science University, 2Portland Alcohol Research Center, 3Department of Veterans Affairs, Portland, OR, USA. Supported by the Department of Veterans Affairs, NIAAA Training Grant 5T32AA07468, Portland Alcohol Research Center Grant P50AA10760, and by an NIAAA Fellowship 1F31AA14070-01.

IBANGS – 19

Anxious-like profile is not associated with higher ethanol self-administration in two pairs of rat lines used as genetic models of anxiety.

G.E. da Silva1, R.N. Takahashi1, A. Ramos2

Clinical evidence points to a positive relationship between anxiety and alcohol abuse. Such an association is supported by some but not all pre-clinical studies. The aim of the present study was to determine whether two pairs of rat lines displaying contrasting levels of experimental anxiety would also differ in their ethanol consumption. Males and females of the Floripa H and L rat lines, selectively bred for high and low central locomotion in the open field, respectively, and the Lewis and SHR inbred rat strains, also known to differ in relation to this and other indices of anxiety/emotionality, were tested in a paradigm of ethanol self administration. Two bottles containing either increasing concentrations of ethanol solution (2% in days 1-4 and 4% in days 5-8) or water were continuously available as a free choice to the animals, with consumption being measured daily. No differences were observed between the Floripa H and L lines for either ethanol intake (g/kg/day) or preference (%), but significant effects ($P<0.05$) of gender (female>male) and day were found within these groups. Lewis rats, on the other hand, in spite of being more anxious-like, were found to consume and prefer less alcohol than their SHR counterparts ($P<0.05$). In these groups, gender (female>male) and day effects were also significant for ethanol intake. The expected association between anxiety and ethanol intake/preference was not found within our genetic models, which suggests that at least some genes that affect one trait may not affect the other. 1Departamento de Farmacologia and 2Departamento de Biologia Celular, Embriologia e Genética, Universidade Federal de Santa Catarina, Florianopolis, SC, Brazil. This work was supported by CNPq, Brazil.

IBANGS – 20

Some common genes underlie GBR-12935 and ethanol sensitivity.

C Reed1, C McKinnon1, S Burkhart-Kasch1, M Huson1, T Phillips1,2

GBR-12935 is a high affinity dopamine reuptake inhibitor that has similar locomotor stimulant properties to ethanol. This experiment tested the hypothesis that sensitivity to the locomotor stimulant effects of GBR-12935 and ethanol is influenced by some common genes. In this experiment, 24 of the BXD recombinant inbred (RI) strains of mice were given saline or GBR-12935 (5 mg/kg or 20 mg/kg) and locomotor activity was monitored. Strain means from this study were then correlated with means from other ethanol-related phenotypes that were collected previously in our laboratory in several (n=21-26) of the same BXD RI mouse strains. Quantitative trait locus (QTL) analysis was performed to provisionally identify loci influencing sensitivity to GBR-12935. These QTL results were compared to those for ethanol-related traits. The QTL analysis identified regions on 12 different chromosomes that were significantly associated with percent change from baseline of locomotor activity after administration of GBR-12935. Several of these QTL locations were common to both GBR-12935 and ethanol-induced locomotor stimulation or ataxia including areas on chromosomes 1, 6, 9, 10, and 11. Previous data from our laboratory have shown a genetic correlation between allopregnanalone sensitivity and ethanol-stimulated activity, as well as common QTL underlying these phenotypes in the BXD RI panel. Thus, both GABAergic and dopaminergic mechanisms appear to influence sensitivity to ethanol's effects on locomotor activity. 1Portland Alcohol Research Center and Department of Behavioral Neuroscience, Oregon Health & Science University, and 2VA Medical Center, Portland, OR USA. This work was supported by: The Department of Veterans Affairs and NIAAA (P50 AA10760).

IBANGS – 21

Methodology for assessing the reinforcing effects of cocaine in mouse strains: comparison of C57Bl/6J and 129 substrains under various schedules of reinforcement.

M Thomsen1,2, SB Caine1

Comparisons among mouse strains including inbred lines and mice with targeted gene mutations may shed light on genes involved in cocaine abuse. However, differences in operant performance rather than in the reinforcing effects of cocaine may contribute to observed differences in cocaine self-administration behavior between genotypes. In addition, strain differences may complicate interpretation of studies of targeted gene mutations created on a mixed background. One objective of the present study is to compare mouse strains commonly used as parental lines for gene targeting, including C57BL/6J and 129 substrains, assessing both food- and cocaine-maintained responding (Caine et al., Psychopharmacology 147:22, 1999). Results of ongoing studies suggest differences between strains in food-maintained responding across a range of liquid food concentrations (peak number of reinforcers per session: C57BL/6J, 98±2, n=12; 129X1/SvJ, 81±6, n=12; 129S6/SvEv, 52±4, n=24). These differences notwithstanding, both C57BL/6J and 129X1/SvJ mice acquiredcocaine self-administration (C57BL/6J, 6 of 6 mice meeting criteria for 1.0 mg/kg/injection; 129X1/SvJ, 11 of 12 mice). In addition, the peak number of cocaine injections (0.1-1.0 mg/kg/injection) earned per session was comparable between groups (43±11, n=6; 48±11, n=9). Ongoing studies will determine whether the dose-effect functions for cocaine self-administration differ between genotypes. Another objective is to further develop techniques for assessing differences in the reinforcing effects of cocaine between mouse strains. First, we are currently evaluating behavior after ³reversal² of the active and inactive manipulanda for cocaine reinforcement. Second, we have optimized a progressive ratio schedule for comparison of operant behaviors in mice. 1Harvard Medical School/McLean Hospital, Belmont, MA, USA and 2Department of Pharmacology, University of Copenhagen, Copenhagen, DK. Supported by NIH/NIDA DA12142, The Lundbeck Foundation and the Zaffaroni Foundation.

IBANGS – 22

QTL analysis of inbred mouse strain differences in a measure of morphine dependence liability.

D McDonough1, C Knowles2, J Bartlet2, E Bilsky2

Morphine has long been a clinically important analgesic but a strong dependence liability limits the situations in which it can be safely used. 129S6/SvEv and C57BL/6J mice show marked differences in both stereotypical locomotor response to morphine and in vertical jumping behavior when morphine withdrawal is precipitated by naloxone despite displaying a similar antinociceptive response to morphine. These differing drug effects indicate that crosses between129S6/SvEv and C57BL/6J may be useful in identifying genes involved in dependence liability but not in antinociception. While morphine produces a robust antinociceptive response in both 129S6/SvEv and C57BL/6J mice, A90 doses of morphine fail to stimulate stereotypic

locomotor activity in inbred strain 129S6/SvEv and even supramaximal doses of morphine produced only very weak increases in locomotor activity in these animals. In contrast, C57BL/6J mice exhibit increasing locomotor activity with increasing dose of morphine on a curve similar to other inbred strains (such as BALB/c) and the ICR outbred strain. Upon naloxone precipitated withdrawal, vertical jumping is far more common in C57BL/6J animals than in 129S6/SvEv animals. We have crossed the 129S6/SvEv and C57BL/6J inbred strains and find that the locomotor response of the F1 animals falls intermediate between the two parental strains. Locomotor response of F2 animals shows a normal distribution indicating that strain differences in locomotor response to morphine should be amenable to QTL analysis in this cross and have begun genotyping F2 animals. The F2 distribution for vertical jumping is heavily skewed towards the non-responding 129S6/SvEv parental phenotype so QTL analysis of this measure will not be pursued. 1Department of Biological Sciences, College of Arts and Sciences and 2Department of Pharmacology, College of Medicine, University of New England, Biddeford, Maine, USA.

IBANGS – 23

A QTL influencing corpus callosum size is located on the X chromosome.

G Kusek, D Wahlsten, L Flaherty

The corpus callosum is the largest fiber tract in the brain that connects the left and right cerebral hemispheres. Corpus callosum size is a complex quantitative trait showing a continuous range of values and is likely influenced by interactions between multiple genes and environmental effects. Reciprocal crosses between BTBR T/+ tf/tf (BTBR) (lacking a corpus callosum) and BALB/cByJ (BALB) (having a corpus callosum) indicate the presence of a gene (or genes) on the X chromosome affecting corpus callosum size. Midsagittal corpus callosum areas were measured in male and female F1 offspring from reciprocal crosses between BTBR and BALB mice. These values were corrected for brain weight. There were significant differences in the size of the corpus callosum between (BTBR x BALB)F1 and (BALB x BTBR)F1 male mice ($p=.0001$), while there was no difference between reciprocal females ($p=.62$). Specifically, the presence of the X chromosome derived from BTBR was associated with a decrease in the mean size of the corpus callosum. In this regard, the X chromosome derived from BTBR appeared to be dominant over the X chromosome derived from BALB. Genomics Institute, Wadsworth Center, 465 Jordan Road, Troy, NY 12180, USA and Dept. of Psychology, BioSci P461, Univ. of Alberta, Edmonton AB Canada T6G 2E9.

IBANGS – 24

The role of a1H T-type Ca2+ channels in multi-modal nociception.

S Choi1, C Chen2, S Lee1, J Lee1, H Seong1, D Kim1, H Lee1, K Campbell2, H Shin1

T-type Ca2+ currents have been implicated in boosting pain signals at the peripheral nervous system and in the spinal cord, but the isotype responsible for the function has not been defined. Here, we examined the behavioral pain responses in mice lacking a1H subunits of T-type Ca2+ channels to diverse noxious stimuli. The mutant mice displayed a significant reduction in pain responses to thermal, (67, 68, and 71 % of wildtype in hot plate, paw withdrawal, and tail flick test, respectively) and mechanical stimuli, (44 % of wildtype in tail clip test), consistent findings with the results of previous studies using T-type blockers. In addition, the mutant showed less pain responses than wildtype in assays both for visceral pain induced by an intraperitoneal injection of acetic acids or MgSO4 and for chronic inflammatory pain induced by a focal injection of formalin (65% of wildtype) in the palm skin. The present study revealed that a1H subunits play a critical role in the multimodal nociception for both somatic and visceral pain, and for chronic pain. These results support the idea that a1H T-type Ca2+ currents contribute to facilitating pain signals at the periphery and in the spinal cord. The modulation of this channel will be a useful strategy for controlling multiple pain responses at the same time. 1National CRI Centre for Calcium & Learning, KIST, Seoul, Korea; and 2Howard Hughes Medical Institute, College of Medicine, University of Iowa, Iowa City, USA.

IBANGS – 25

Aggression, impulsivity, and the dopamine D4 receptor in the canine model.

GJ Golden1, BS Kwon1, KA Houpt2, TA Houpt1

Based on human genetic studies, it has been suggested that impulsivity and aggression is correlated with the presence of polymorphisms in the dopamine D4 receptor (DRD4) gene. Dogs are an appealing model to test this hypothesis because 1) unlike rodents, they possess an exon III repeat polymorphism homologous to

humans and 2) they present for idiopathic aggression. Therefore, we are screening aggressive dogs for DRD4 polymorphisms, and cloning the canine DRD4 gene.To establish clinical correlations, we are genotyping aggressive dogs presenting for behavior problems at the Cornell Animal Behavior Clinic and non-aggressive dogs presented for annual check-ups. DNA was extracted from whole blood using phenol-chloroform extraction. Using primers that flank the repeat polymorphism, a section of the DRD4 gene was amplified (HotStarTaq Master M! ix!, Qiagen). Across 45 dogs, three PCR products (273, 285, and 285) were found that correspond to the alleles A, B and C of Niimi et al., 1999. Genotyping is ongoing and the work is currently inconclusive. In order to clone the canine DRD4, DNA was extracted from Golden Retriever liver. Using primers based on the human sequence (Van Tol et al., 1991), an 1851 bp fragment from exon I to exon III including two introns (corresponding to the human DRD4 bases 141 to 2816) was amplified, cloned, and sequenced. Analysis of the exon III-IV fragment is ongoing. There is a 92-98% identity of exons I-III to the human exonic sequence with no similarity between the canine and human introns. From the genomic sequence we will be able to establish chromosomal markers for use in the analysis of aggressive pedigrees. 1Neuroscience Program, Florida State University, Tallahassee, FL 32306, USA. 2College of Veterinary Medicine, Cornell University, Ithaca, NY 14850, USA.

IBANGS – 26

Changes in gene expression of serotonin receptors in a mouse model of aggression.

S Chiavegatto1,2, T Bibancos1, I Aneas2, HP Vallada1

We are now investigating the gene expression profile of multiple brain regions in groups of male adult C57BL/6J mice that differ in their responsiveness to an intruder in their home cages. It is known that the level of aggressiveness in mice is enhanced after repeated exposures to the resident-intruder paradigm. In our model, there is a remarkable increase in the aggressive behavior of the isolated resident mice after 4 exposures of 15 min to an intruder in a 3-day interval between each exposure ($p<0.05$). We then selected 2 groups of animals based on aggression indices (e.g., number of attacks, latency): the highly aggressive (A) and the non-aggressive residents (NA; $p<0.001$). Mice from both groups were sacrificed about 3 h after the last exposure to the intruder and the RNA immediately isolated from the hippocampus, hypothalamus, frontal cortex and cerebellum. The differential expression of several genes in these brain areas was revealed by cDNA and oligo microarrays and is currently being validated by an independent technique. The serotonin system is widely involved in aggressive behavior. Since microarrays have reduced sensitivity to less abundant genes and to small alterations in gene expression that frequently occur in the brain, we are investigating the serotonin receptors 5-HT1A, 5-HT1B, 5-HT2A and 5-HT2C in these mice by RealTime RT-PCR. While no alterations are found in the cerebellum, a region not directly implicated with aggressive behavior, changes in the expression of some 5-HT receptors are observed in the hippocampus. 1Institute of Psychiatry and 2Heart Institute (InCor), School of Medicine, University of Sao Paulo, SP, Brazil. Supported by FAPESP (01/01637-5 and 01/09079-1) to SC.

IBANGS – 27

Searching for genes in the flanking regions of knockout/congenic strains.

VJ Bolivar, L Flaherty

Knockout mice are usually generated from 129 embryonic stem cells. The resulting progeny are then often backcrossed to B6 for a number of generations, resulting in a knockout/congenic strain. Although most background genes are derived from B6, the region flanking the target gene remains 129 in origin. Thus, these knockout/congenic strains represent a potential resource for mapping genes surrounding the target locus, as long as there are phenotypic and genotypic differences between B6 and 129. Our laboratory is currently using these strains to look for genes involved in complex behaviors. We recently completed a survey of knockout/congenic mouse strains. Mice were evaluated in two behavioral assays, open field behavior and fear conditioning. Twenty-four males of each strain were tested. Several knockout/congenic strains performed differently from B6 in one or both of these behavioral assays and are being investigated further. One strain of interest is Il7r, a B6-congenic strain where the proximal end of Chromosome 15, an area rich in behavioral QTLs, is derived from 129. We are currently conducting studies to determine whether the behavioral effects seen in this strain are due to the flanking region or the target gene itself. We are also examining a pair of knockout/congenic strains developed by two different laboratories, both targeting the Cd4 gene (Chromosome 6). We found behavioral differences between these two strains and are currently

determining the size of the flanking regions. Genomics Institute, Wadsworth Center, Troy, NY, USA. This research was supported by the National Institutes of Health.

IBANGS – 28

Antidepressant actions of citalopram and milnacipran in C57BL/6J and 129S6/SvEv inbred strains of mice.

T Marks1, ZJ Trzaska1, N Dube1, CJ Knowles1, S Rao2, and EJ Bilsky1

Selective transport inhibitors and transgenic and knockout (KO) rodent models for the serotonin and norepinephrine transporters (5-HTT and NET, espectively) have provided key insight into the molecular mechanisms of antidepressants. A recent paper was able to differentiate the importance of the 5-HTT and NET in mediating the antidepressant effects of fluoxetine, desipramine and imipramine in mice (Holmes et al., Neuropsychopharmacology, 27:914-23, 2002). The paper also highlighted the influence of background strains of mice in the behavioral phenotyping of KO animals. We report here on the antidepressant actions of citalopram (5-HTT>>NET) and milnacipran (NET>5-HTT) in C57BL/6 and 129S6/SvEv, two inbred strains commonly used to generate knockout animals. Milnacipran dose-relatedly decreased immobility in the mouse forced-swim test (FST) in both strains, though it was less potent in the 129S6/SvEv strain. In contrast, citalopram potently increased immobility time in the 129S6/SvEv strain without having a major effect on locomotor activity. These results support and extend previous findings in 5-HTT KO mice that were backcrossed onto the 129S6/SvEv background. The data also continue to highlight the very interesting 129S6/SvEv genotype and phenotype, especially to the field of neuropharmacology. 1Department of Pharmacology, University of New England College of Osteopathic Medicine, Biddeford, ME, USA, 2Cypress Bioscience Inc., San Diego, CA, USA. This research was supported in part through funds provided by Cypress Bioscience Inc.

IBANGS – 29

The behavioral actions of alcohol exhibit GABAA receptor subunit specificity: Evidence from α2 and α5 null mutant mice.

SL Boehm II1, AW Jennings1, P Whiting2, T Rosahl2, E Garrett2, YA Blednov1, RA Harris1

GABAA receptors are pentameric ligand-gated ion channels thought to mediate several behavioral actions of alcohol. Currently, seven different receptor subunit classes have been discovered (α1-6, β1-3, γ1-3, ρ1-3, δ, ε, σ), and the presence of certain subunits have profound effects on receptor pharmacology. Indeed, pharmacological data suggest that α5 subunits mediate alcohol's reinforcing properties (June et al., 2001). Moreover, whereas the behavioral actions of alcohol have not yet been studied, α2-receptor subunits may mediate the anxiolytic effects of benzodiazepines (Low et al., 2000). We examined sensitivity to several of alcohol's behavioral actions in GABAA α2- and α5-receptor subunit null mutant mice. We predicted that deletion of the α2 gene would reduce sensitivity to alcohol's anxiolytic effects, whereas null mutation of the α5 gene would reduce sensitivity to alcohol's reinforcing properties. Deletion of the α5 subunit gene resulted in reduced alcohol preference drinking in a two-bottle choice paradigm, whereas deletion of the α2 subunit gene did not. Moreover, α2 null mutants exhibited enhanced sensitivity to alcohol's sedative hypnotic effects (loss of righting reflex). In contrast, α5 null mutants did not differ in sensitivity to this behavioral effect of alcohol. Studies investigating the reinforcing properties of alcohol using conditioned place preference, and the anxiolytic effects of alcohol using the elevated plus maze, are underway. Thus, considered along with other published data on alcohol sensitivity in GABAA α1- and β2-receptor subunit null mutant mice (Blednov et al., 2002), the current studies suggest that different behavioral actions of alcohol are mediated by specific GABAA receptors subunits. 1Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin, Austin TX, USA. 2Merck Sharp and Dohme, Harlow, UK. These studies are supported by NIAAA grants AA07471, AA13520, AA06399.

IBANGS – 30

Haplotypic block on mouse Chromosome 7 associated with modifications in the pharmacology of benzodiazepines.

L Prut1, G Chapouthier2, AM Le Guisquet1, S Marouillat3, C Andres3, C Belzung1

Benzodiazepines are widely prescribed drugs. They induce a large number of effects, including anxiolytics, myorelaxant, sedative, anticonvulsivant and amnestic ones. In the past years, some of these effects have

been associated with some precise sub-units of the GABA-A pentamer, particularly with the a-subunits. ABP/le is an inbred strain of mice carrying various markers; the presence of these markers can be easily detected because they induce the expression of some morphological features. One of these markers is the pink-eyed dilution gene (p); that corresponds to a gene located on the mouse chromosome 7, at 0.5cM of the Gabra5 gene encoding for the a5-subunit of the GABA-A receptor. When crossing mice from the ABP strain with mice from the C57BL/6 strain, one can obtain pp mice in the F2 generation that express the p marker and not the other markers of the ABP/le strain. In the present study we compared the effects of chlordiazepoxide in WT and pp mice confronted to two tasks: the radial arm maze in order to test for the chlordiazepoxide amnestic effects and the rotarod that enabled to assess the myorelaxant properties of the benzodiazepine. Results show that, when compared to WT animals, pp mice are not sensitive to the amnestic and myorelaxant effects of chlordiazepoxide. This modification is associated with 9 polymorphism on the Gabra5 gene. Even if the mutations do not induce any modification of the a5-subunit protein, one may argue that an haplotypic block on mouse chromosome 7 may be associated with modifications in the pharmacology of benzodiazepines. 1) EA3248, Tours, France, 2) UMR 7593, Paris, France, 3) U316, Tours, France.

IBANGS – 31

A phenotypic and molecular characterization of the fmr1-tm1Cgr Fragile X Mouse.

QJ Yan1, PK Asafo-Adjei1, HM Arnold3, RE Brown2, RP Bauchwitz1

Fragile X Syndrome is the most common form of inherited mental retardation. Fragile X Syndrome is also known for having a substantial behavioral morbidity, including autistic features. It is almost always caused in humans by inactivation of the X-linked FMR1 gene. A single knockout mouse model, fmr1-tm1Cgr, exists. In this report we further characterize the cognitive and behavioral phenotype of the fmr1-tm1Cgr Fragile X mouse through the use of F1 hybrid mice derived from two inbred strains. Use of F1 hybrids allows focus on the effects of the fmr1-tm1Cgr allele without undue influence of recessive alleles present in the parental inbred strains. We find that the cognitive phenotype of fmr1-tm1Cgr mice, including measures of working memory and learning set formation which are known to be seriously impacted in humans with Fragile X Syndrome, are essentially normal. Further testing of inbred strains supports this conclusion. Thus, any fmr1-tm1Cgr cognitive deficit is surprisingly mild or absent. There is, however, clear support presented for a robust audiogenic seizure phenotype in all strains tested, as well as open field behavior which may reflect other aspects of hyperarousal. Finally, a molecular examination of the fmr1-tm1Cgr mouse shows that, contrary to common belief, it is not a molecular null. Implications of this finding for interpretation of the phenotype are discussed. 1Department of Neurology, St. Luke's-Roosevelt Institute of Health Sciences, Columbia University, New York, NY, USA, 2Department of Psychology, Dalhousie University, Halifax, Nova Scotia, Canada, 3Behavioral Neuropharmacology, Sention, Inc., Providence, RI, USA. Funded by the FRAXA Research Foundation.

IBANGS – 32

Acquisition of an operant go-no go task in transgenic mice overexpressing galanin.

CC Wrenn, MC Saavedra, JN Crawley

Galanin is a neuropeptide that is overexpressed in the nucleus basalis of Alzheimer's disease patients. This overexpression of galanin may contribute to the cognitive deficits of Alzheimer's disease. Support for this hypothesis has come from the consistent body of literature showing that central microinjection of galanin produces cognitive deficits in rats. Further, transgenic mice that overexpress galanin (GAL-tg mice) show performance deficits in spatial, olfactory, and fear conditioning learning and memory tasks. In the present study, we tested the ability of GAL-tg mice to acquire a simple go-no go operant task. In this task, mice were trained to nose poke for an Ensure liquid diet food reward when the nose-poke hole was illuminated (go task). After acquisition of this contingency, attentional function was assessed by decreasing the duration of illumination. Finally, attention and impulsivity were assessed by training the mice to withhold responding whenever a tone was presented simultaneously with the illumination of the hole (no go task). GAL-tg mice did not differ from wildtype littermate controls in the acquisition of the go task, performance when illumination duration was decreased, or in the acquisition of the no go task. These data show that GAL-tg mice can acquire simple operant tasks. Laboratory of Behavioral Neuroscience, National Institute of Mental Health, Bethesda, MD, USA.

IBANGS – 33

Histidine-decarboxylase knockout mice show deficient non-reinfoced episodic object memory, improved negatively reinforced water-maze performance and increased neo- and ventro-striatal dopamine turnover.

E Dere1,3, MA de Souza-Silva1,3, B Topic1,3, RE Spieler4, HL Haas2,3, JP Huston1,3

The brain's histaminergic system has been implicated in hippocampal synaptic plasticity, learning and memory as well as brain reward and reinforcement. Our past pharmacological and lesion studies suggested that the brain's histamine system exerts inhibitory effects on the brain's reinforcement respective reward system reciprocal to mesolimbic dopamine systems, thereby modulating learning and memory performance. Given the close functional relationship between brain reinforcement and memory processes, the total depletion of brain histamine via genetic inactivation of its synthetisizing enzyme histidine decarboxylase (HDC) in the mouse might have differential effects on learning dependent on the task-inherent reinforcement contingencies. Here, we investigated the effects of a HDC gene-inactivation in the mouse in a non-reinforced object exploration task and a negatively reinforced water-maze task as well as on neo- and ventro-striatal dopamine systems known to be involved in brain reward and reinforcement. HDC-KO mice had a higher DOPAC concentration and higher DOPAC/DA ratio in the neostriatum. In the ventral striatum the DOPAC/DA and 3-MT/DA ratio was higher in HDC-KO mice. Furthermore, the HDC-KO mice showed improved water-maze performance during both hidden and cued platform tasks, but deficient object discrimination based on temporal relationships. Our data suggest that depletion of brain histamine can have both memory promoting and suppressive effects via distinct and independent mechanisms and further suggest that these opposed effects are related to the task-inherent reinforcement contingencies. Supported by the Deutsche Forschungsgemeinschaft. 1Institute of Physiological Psychology, and 2Institute of Neurophysiology, 3Center for Biological and Medical Research, University of Düsseldorf, D-40225 Düsseldorf, Germany. 4Oceanographic Center, Nova Southeastern University, Dania, FL, USA.

IBANGS – 34

Gene targeting reveals a new role of GDNF in memory.

R Gerlai

Gene targeting has been frequently used to investigate the potential contribution of genes to different aspects of brain function. However, the technology has been heavily criticized. The issues center around two main problems: the "flanking allele" problem and compensatory mechanisms. A study is presented here in which the first issue is resolved and the interpretive problems due to compensatory mechanisms are discussed. Heterozygous knockout mice carrying one null allele of the gene encoding the glial cell line-derived neurotrophic factor (GDNF) are analyzed. GDNF was known to exert survival-promoting effects on dopaminergic neurons, however, a role of endogenous GDNF in brain function and behavior has not been established. Behavioral and neurochemical tests sensitive to deficits in either nigrostriatal or hippocampal function are conducted. Surprisingly, both neurochemical and behavioral measures suggest that mutant mice possess an intact nigrostriatal dopaminergic system. However, mutant mice exhibit a significant and selective impairment in the spatial version of the Morris water maze, a cognitive task sensitive to hippocampal dysfunction. These results imply that endogenous GDNF plays an important role in mammalian brain function and/or development affecting cognition. In conclusion, the study demonstrates that when the technical and principal problems of gene targeting are considered appropriately, this technology allows the investigator to reveal fundamentally new pieces of information about the role particular genes play in higher brain function. Univ of Hawaii, Honolulu, Hawaii, USA.

IBANGS – 35

Enhanced learning and memory in mice lacking Na+/Ca2+ exchanger 2.

D Jeon1, H Lee1, Y-M Yang2, M-J Jeong1, KD Philipson3, H Rhim2, H-S Shin1, 4

The plasma membrane Na+/Ca2+ exchanger (NCX) plays a role in regulation of intracellular Ca2+ concentration via the forward mode (Ca2+ efflux) or the reverse mode (Ca2+ influx). To define the physiological function of the exchanger in vivo, we generated mice deficient for NCX2, the major isoform in the brain. Mutant hippocampal neurons exhibited a significantly delayed clearance of elevated Ca2+ following depolarization. The frequency threshold for LTP and LTD in the hippocampal CA1 region was

shifted to a lowered frequency in the mutant mice thereby favoring LTP. Behaviorally, the mutant mice exhibited enhanced performance in several hippocampus-dependent learning and memory tasks. These results demonstrate that NCX2 can be a temporal regulator of Ca2+ homeostasis and as such is essential for the control of synaptic plasticity and cognition. 1National Creative Research Initiative Center for Calcium & Learning, and 2Center for Medical Science Research, Korea Institute of Science and Technology, Seoul, Korea. 3Cardiovascular Research Laboratories, UCLA School of Medicine, Los Angeles, CA, USA 4Correspondence to: Hee-Sup Shin, MD, PhD.

IBANGS – 36

Improved spatial learning on a modified Morris water maze is genotype dependent.

D Wahlsten1,2, SF Cooper1, JC Crabbe3,4

The circular water maze with a submerged platform is a widely used method for assessing spatial memory deficits in mice. Because mice adapt to this task in varied ways, sophisticated videotracking and path analysis are needed to decipher the message in the swim path, and nonspatial tendencies can sometimes obscure the memory factor. A recent study observed that CREB knockout mice were deficient in learning the maze because they were more likely to hug the walls of the water tank. Whether mice that hug the walls of the tank also have deficient spatial memory thus cannot be assessed with the standard Morris maze. We have evaluated more than a dozen variants of the submerged platform task and compared them with the conventional Morris maze. We present here a simple alternative to the Morris task, a 4-arm maze, which reveals competent spatial learning even in wall-hugging strains. Moreover, the 4-arm maze does not require probe trials, and can easily be scored by an observer without the use of complex videotracking equipment. 1Dept of Psychology and 2Centre for Neuroscience, University of Alberta, Edmonton AB Canada, 3Dept of Behavioral Neuroscience, Oregon Health & Science University, and 4Portland Alcohol Research Center, VA Medical Center, Portland OR USA. Supported by NIH grants R01 AA10760 and AA12714, NSERC grant 45825, and a grant from the Department of Veterans Affairs.

IBANGS – 37

Survival of hippocampally lesioned mice in outdoor pens: equal magnitude of lesion and genotype effects.

DP Wolfer1, R Deacon2, JNP Rawlins2, MG Pleskacheva3 AL Vyssotski1, I Amrein1, P D'Adamo1, H-P Lipp1

In order to study the effects of hippocampal lesions on the ability of survival under semi-naturalistic conditions, 23 female mice received either sham surgery or bilateral cytotoxic lesions of the entire hippocampus by means of multiple slow injections of NMDA into the hippocampus. Stereotaxic injections were done in a field station in western Russia. 14 mice (6 controls, 8 hippocampals) were of pure C57BL/6 background , while 9 mice were selected from a randomly bred stock derived from a diallel cross between strains C57BL/6, DBA/2, NZB and C3H. After recovery, mice were tagged with passive transponders permitting electronic identification and released into an outdoor pen of 10x10 m containing two shelters of 2x2 m for protection. Inside the pen, 8 transponder antennae recorded mice visiting these locations. Food was placed first at two locations within the shelters, and then at various antenna sites outdoors. A computer system monitored visits over a period of 39 days. Hippocampal mice appeared rapidly at the within-shelter feeding sites, but were significantly slower to appear at the first outdoor feeding places. The most surprising finding resulted from a Kaplan-Meyer analysis of survival: as expected, mice with hippocampal lesions disappeared earlier from the pen ($p < 0.05$). However, the genotype of the lesioned mice played a remarkable role. Lesioned mice with a C57 background disappeared most rapidly, but the survival of C57 control mice was not better than survival of lesioned mice with a mixed genetic background. These findings underline the importance of hybrid vigor in survival ability and imply that being a C57BL/6 mouse in an outdoor pen is about equally risky as being a mouse with mixed genetic background yet lacking both hippocampi. 1Division of Neuroanatomy and Behavior, Institute of Anatomy, University of Zurich, Switzerland. 2Department of Psychology, University of Oxford, UK. 3Laboratory of Physiology & Genetics of Behavior, Moscow State University, Russia. This work was supported by Swiss National Foundation and the NCCR "Neural Plasticity and Repair".

IBANGS – 38

The structure and heritability of cross-arena traits in cognitive and exploratory batteries for mice.

MJ Galsworthy, R Madani, JL Paya-Cano, L Liu, C Fernandes, LC Schalkwyk, R Plomin, H-P Lipp, DP Wolfer

This report presents analyses of cross-task individual differences in two separate studies; firstly, analyses of cognitive tasks from the London laboratory, and secondly, a meta-analysis of exploratory tasks from the Zurich laboratory. In the first study, 84 male sibling pairs (total N=168) from a population of heterogeneous stock (HS) mice were run on seven different cognitive arenas: T-maze, Morris maze, water plus maze, Hebb-Williams maze, two puzzle boxes, and an object exploration task. Measures from these diverse arenas all loaded positively on the first factor in principal component factor analysis, nominating the presence of a general cognitive ability in mice. This g-factor accounted for approximately 24% of the variance, similar to our previous study of 84 HS mice. A robustness analysis showed this factor structure to be very stable to permutations of the battery and sibling correlations indicated a 'crude heritability' of 42% for the g-factor derived from the battery. In the second study, >4,200 mice of inbred, hybrid, mutant and outbred genotypes ran one or more of five exploration tasks. Of the 1,966 individuals that ran more than one procedure, 764 ran the open field, null maze and light-dark box, 1285 ran the emergence test and novel object test, and 367 ran all five tests. In this last group, individual consistency in exploratory movement type across all arenas was examined. Proportion of time engaged in scanning movement correlated positively amongst the arenas (first factor accounting for 32% of variance), similarly for resting (53%) and progressing (63%) measures. Other analyses to be also presented. Conclusions centre on the reliabilities of mouse behaviour and the use of factor analysis in a confirmatory context to clarify cross-arena traits and the measures that best inform on these traits. Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College London, UK, and Division of Neuroanatomy and Behavior, Institute of Anatomy, University of Zurich, Switzerland. This work was supported in part by the Swiss National Foundation and NCCR "Neural Plasticity and Repair".

IBANGS – 39

Interpretation of results of learning and memory test batteries in mice: Is it intelligence, or anxiety, locomotion, body weight, visual acuity, deafness that we are measuring?

RE Brown, L Standford, M Williamson, AA Wong, M Arnold

We have tested 16 strains of mice in a battery of tests for anxiety, locomotion, and exploration (elevated plus maze, light-dark box, open field), spatial memory (water maze, Barnes maze), motor learning (rotarod), object recognition memory and olfactory memory. Our aim is to examine the factor structure of the memory tests. However, we have found that the results of some tests are influenced by non-cognitive factors such as body weight, visual acuity, hearing ability, anxiety, exploratory behaviour and locomotion. How many of the results of mouse learning and memory tests are artifacts of sensori-motor differences and how do we determine the true measure of cognitive performance in mice? In this presentation, we discuss our struggle to answer the question of how these non-cognitive factors affect our measures of learning and memory and how to develop measures of mouse intelligence which are unaffected by body weight, blindness, deafness and other sensori-motor deficits. Psychology Department, Dalhousie University, Halifax, NS, Canada B3H 4J1. Supported by grants from NSERC of Canada, the March of Dimes and the JAX Phenome project.

IBANGS – 40

Retinoic acid (Accutane) affects hippocampal dependent learning and neurogenesis in mice.

YS Mineur, D Prasol, P McCaffery, JE Crandall, WE Crusio

Numerous clinical studies have associated the use of the oral acne drug Accutane (Isoretinoin, 13-cis retinoic acid, RA) with broad and variable side-effects on behavior that include headache and depression. Since RA enters the CNS and can act as a potent transcriptional activator for many genes, it is quite plausible that RA influences brain function and structure. Indeed, in a different experiment we found that chronic exposure to RA influenced proliferation in the hippocampus. In the first set of behavioral experiments we injected male CD1 mice i.p. with 13 cis RA at 1 mg/kg (the standard dose for oral Accutane treatment) daily for 28 days and tested them for levels of anxiety in a light-dark box, aggression in a resident-intruder test, learning in a spatial radial maze, and in two paradigms that are sensitive to antidepressant drugs: the tail-suspension and startle reflex tests. Results showed a dramatic decrease in learning capabilities in the

radial maze test, but no significant effects in any other behavioral assay. In a second set of experiments, we treated male mice from the inbred strains C57BL/6J and DBA/2J with the same dose of RA for the same length of time and tested them for levels of anxiety in a plus maze, learning in a cued and contextual fear conditioning test, and in three tests for depression: the tail suspension test, the Porsolt test, and the startle reflex test. Large significant strain differences were found for all behaviors tested. The only treatment-related effect was a trend towards a decrease in hippocampus-dependent contextual fear conditioning. These data imply that chronic RA exposure selectively affects hippocampal dependent learning, which could potentially be related to the change in cell proliferation in the adult hippocampus. Brudnick Neuropsychiatric Research Institute, University of Massachusetts Medical School, Worchester, MA, USA. Supported by NIH grant MH66037.

IBANGS – 41

Inhibitory processing of startle responses to acoustic and tactile stimuli mediated by T-type calcium channels.

J Lee1, S Choi1, D Kim1. S Oh2, H Shin1

Three a1 subunits of T-type Ca+2 channels, G, H, and I, are differentially expressed in the pathways for the sensory transduction including peripheral sensory neurons, the spinal cord, and the thalamus. Previously, we showed that a1G T-type Ca+2 channels play a critical role in the generation of burst firing in the thalamus and thereby contribute to inhibitory processing of noxious signals originated from the viscera, causing enhanced pain behavior in a1G knockout mice. However, their contribution to other sensory modalities remains unknown. To address this, we examined startle response of a1G knockout mice to acoustic or tactile stimulus. To increasing intensities of sound delivered, wild type mice showed the first startle response at 100 dB and the amplitude of startle increased up to 120 dB. Mutants had a similar threshold of startle response at 100 dB, but they showed significantly higher amplitude than that observed in the wild type at the same intensities of the sound delivered. Such difference between genotypes, however, was not observed in the auditory brainstem response evoked by “click” sound within the amplitude varying from –20dB to 90dB, indicating no alteration in the primary sensory pathway in mutants. In response to tactile stimulus elicited by air-puffing on 12 psi, mutants also showed enhanced startle. The present results suggest T-type Ca+2 channels play an inhibitory role in the startle response to tactile and acoustic stimuli. Along with the findings of the enhanced visceral nociception, these results suggest that T-type Ca+2 channels contribute to the multi-modal sensory processing independently from the peripheral mechanism. 1National CRI Centre for Calcium & Learning, KIST, 2Department of Otorhinolaryngology-Head and Neck Surgery, College of Medicine, Seoul National University, South Korea.

IBANGS – 42

Acoustic habituation and tactile habituation of the startle response are independent processes.

CF Plappert, PKD Pilz

One of the simplest forms of learning is habituation, defined as response decrease to repeated stimulation. Habituation of the startle response can be evoked by acoustic and tactile stimuli. The underlying pathways of the acoustic (ASR) and the tactile startle response (TSR) consist of a common central element, the PnC (nucleus reticularis pontis caudalis), where afferent projections from both sensory branches terminate. The efferent motor branch from the PnC is shared in both, ASR and TSR. The present study sought to inspect whether habituation occurs in the sensory afferents or the common efferent part of the startle pathway. Therefore, ASR and TSR were habituated, and it was tested whether habituation generalizes from one modality to the other. A) TSR habituation, ASR test: 12 C57BL/6J male mice were given 100 tactile stimuli (air puffs, 0.091 psi, 100 dB background noise to mask the acoustic component of the air puff), followed by 50 acoustic stimuli (14 kHz, 115 dB, ISI 15 sec, 45 dB background noise); control: ASR test was preceded by the TSR-condition without tactile stimuli. B) ASR habituation, TSR test: 100 acoustic stimuli (control: respective pause) were followed by 50 tactile stimuli. Similar tests were conducted with BALB/cAN and DBA/2N mice. The course of startle amplitude was identical with and without prior habituation by the respective different modality, for both ASR and TSR, and for all three strains. Thus, no generalization of habituation occurred across the modalities. This means that the habituation of the startle response obviously occurs in the sensory afferents to the PnC. Animal Physiology, University of Tuebingen, Morgenstelle 28,

72076 Tuebingen, Germany. This work was supported by the Deutsche Forschungsgemeinschaft (DFG, Schn 23/1-4).

IBANGS – 43

Dopaminergic regulation of prepulse inhibition in mice and rats: strain and species differences and similarities.

RJ Ralph-Williams, SB Caine

Recent studies with inbred mice suggest there may be strain and/or species differences in the dopaminergic modulation of prepulse inhibition of startle (PPI) among rodents. To further examine this hypothesis, we tested inbred 129X1/SvJ, C57BL/6J, and DBA/2J mice, and outbred Swiss Webster mice and outbred Sprague Dawley rats, treated with the D1 agonist R-6-Br-APB (0.032-3.2 mg/kg) or the D2 agonist quinelorane (0.01-0.32 mg/kg). In additional studies, we pretreated the animals with either the D1 antagonist SCH39166 or the D2 antagonist eticlopride (1 mg/kg). The D1 but not the D2 agonist dose-dependently reduced PPI in 129X1/SvJ, C57BL/6J, and Swiss Webster mice. In contrast to all those mouse strains, and consistent with previous reports in rats, the D2 agonist dose-dependently reduced PPI in Sprague-Dawley rats. Interestingly, pretreatment with either the D1 or the D2 antagonist prevented the PPI-disruptive effects of the D1 agonist in mice and the D2 agonist in rats. DBA/2J mice differed from the other mice and rats ? a low dose of the D2 agonist and the D2 antagonist both increased PPI, the latter being consistent with previous studies in DBA/2J mice. Taken together, our results suggest species differences such that the D1 receptor has a more prominent role than the D2 receptor in the modulation of PPI in several inbred strains and an outbred strain of mice, whereas the reverse is true in outbred Sprague-Dawley rats. In addition, our findings suggest similarities between these strains of mice and rats such that D1/D2 receptor interactions are revealed when one receptor is blocked while the other receptor is stimulated. Harvard Medical School/McLean Hospital, ADARC, 115 Mill Street, Belmont, MA, USA. Supported by NIH/NIDA (DA07252) and the Zaffaroni Foundation.