INTERNATIONAL BEHAVIOURAL AND NEURAL GENETICS SOCIETY

8th Annual Meeting
May 19-22, 2006
University of British Columbia
Vancouver, Canada

Conference Program and Abstracts

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 Inst of Health, USA
Exhibitor: ViewPoint Life Sciences Inc, Montreal, Canada

Special thanks to –

Program Committee: Daniel Goldowitz (chair), Tamara Phillips, Nina Popova, Inga Poletaeva, and Catharine Rankin
Local Organizer: Catharine Rankin, with great assistance by Mark Rutledge-Gorman
UBC Conferences and Accommodations: Mariela McIlwraith and Karen Stefanson

CONFERENCE PROGRAM

International Behavioural and Neural Genetics Society (IBANGS)

Friday, May19

15:00-18:00 On-site registration available in Gage Tower, Ruth Blair A
18:00-20:00 Opening Gala Reception at Kenny Bldg, Dept of Psychology (Registration Available on site.)

Saturday, May 20

07:30-08:30 Continental Breakfast at Buchanan Lower Lobby
POSTERS!!! **(Posters may be put up on Saturday morning and stay up all day)**
07:30-16:00 Registration available (Buchanan Lower Lobby)
08:30-08:45 Opening Remarks Buchanan 100 (location of all talks)
SPEAKERS: note to all speakers: Please go to the lecture hall one half hour before your talk to load your talk on the computer and ensure that everything is working

08:45-10:00 **Presidential Plenary Address** by Dr. Susumu Tonegawa, Howard Hughes Medical Institute, Massachusetts Institute of Technology, USA, "**Molecular, cellular, and circuit mechanisms for hippocampal memory"**

10:00-10:30 Coffee Break

10:30-12:30 **Symposium I: From mouse genetics to genomics to behavior: 35 years of progress. A symposium to honor the winner of the 2005 IBANGS Distinguished Scientist Award, Dr. Lorraine Flaherty**; Chair: Douglas Wahlsten

Gene Rinchik -Taconic Farms, Inc., Hudson, New York, USA - *Common themes from my 30 years with Lori Flaherty*

Valerie Bolivar - Wadsworth Center, New York State Department of Health, Troy, New York, USA - *Dissecting behavior: The power of mouse genetics*

Melloni Cook – University of Memphis, Tennessee, USA – *Of mice and Lori: Simple lessons in genetics, friendship and courage*

Gretchen Kusek - University at Albany, State University of New York, New York USA - *X Chromosome control of corpus callosum formation*

12:30-12:45 Symposium I discussion

12:45-14:00 Lunch

14:00-16:00 **Paper Session** (speaker is underlined and speaker's institution is listed)
Chair Inga Poletaeva

Oliver Ambrée, N Görtz, A Herring, N Sachser, W Paulus, K Keyvani – University of Münster, Germany - *Environmental enrichment reduces Aβ deposition in a transgenic mouse model of Alzheimer's disease: Involvement of multiple processes*

Eunji Cheong, S Lee, J Choi, M Sun, C Lee, H-S Shin – Korea Institute of Science & Technology, Seoul, Korea - *The molecular switch of thalamic sensory gating*

P Stafford, F Casidy, J Badger, C Zhao, S Roche, P McKeon, Seth Dobrin - Center for Medical Genetics, Marshfield Clinic, Marshfield, Wisconsin

USA – *Genetics and genomics of Bipolar Disorder: Combining multiple data types and generating meaning from the mania*

Mary-Anne Enoch, K White, J Waheed, X-Z Hu, C Harris, D Goldman - National Institute on Alcohol Abuse and Alcoholism, NIH, USA – *Differences in genetic origins and attentional responses between pure and comorbid anxiety disorders in humans*

Christopher Kliethermes, J Crabbe - University of California-San Francisco, USA – *Behavioral, pharmacological, and gene expression differences between lines of mice bred for differences in exploratory behavior*

David Segal, K Walder, M Malakellis, A Sanigorski, G Collier - *Deakin University, Waurn Ponds, Australia – Large scale gene expression analysis in the hypothalamus of an animal model of depression*

Douglas Swanson, E Brauer, G Ramirez, M Butler, E Polosetsky, Y Benjamini, I Golani, D Goldowitz - University of Tennessee, Memphis, USA – *A neuroethological approach to dissecting the roles of cerebellar purkinjie cells in open field behavior*

Michael Butterfield, C Rankin – University of British Columbia, Canada - *The effects of stimulation and ethanol exposure on long-term memory training in* C. elegans

16:00-18:00 Poster Session in Buchanan Lower Lobby

Sunday, May 21

07:30-08:30 Continental Breakfast (Buchanan Lobby)

07:30-17:00 Registration available (Buchanan Lobby)

SPEAKERS: **note to all speakers: Please go to the lecture hall one half hour before your talk to load your talk on the computer and ensure that everything is working**

08:45-10:00 **Plenary Address by Distinguished Scientist Award recipient** Dr. Douglas Wahlsten, University of Windsor, Ontario, Canada, "**Genetic heritability: An old bottle for some 21st century wine"** (Buchanan 100)

10:00-10:30 Coffee Break

10:30 -12:30 **Symposium II: Emotion, play, and dominance**; Chair: Gareth Lahvis

Michel Cabanac - Laval University, Quebec, Canada - *Threshold of consciousness in phylogeny*

Gordon Burghardt - University of Tennessee, Knoxville, USA - *The origins of vertebrate play: A role for the heritability of experience*

Gareth Lahvis - University of Wisconsin, Madison, USA – *Motivations for social approach behaviors among juvenile* Mus musculus

Jaak Panksepp - Washington State University, Pullman, USA - *Ultrasonic vocalizations as indices of affective states in rats and associated genetic consequences*

12:30-12:45 Symposium II Discussion

12:45-14:00 Lunch

14:00-16:00 **Symposium III: Mouse sensory systems and behaviour**; Chair: Richard Brown

Aimee Wong - Dalhousie University, Halifax, Nova Scotia, Canada - *The influence of visual ability on the behavior of mice in a battery of tests*

Richard Brown - Dalhousie University, Halifax, Nova Scotia, Canada - *Olfaction and mouse behaviour*

Sandra McFadden - Western Illinois University, Macomb, Illinois, USA - *Hearing and mouse behavior*

Alexander Bachmanov - Monell Chemical Senses Center, Philadelphia, Pennsylvania, USA - *Taste and behavior in mice*

Shad Smith - McGill University, Montreal, Quebec, Canada - *Genetic variability and considerations for pain measurement in inbred and transgenic mice*

Richard Dyck - University of Calgary, Alberta, Canada - *Vibrissa function and somatosensory cortex plasticity in mice*

16:00-16:15 Symposium III Discussion

16:15-17:15 IBANGS Business Meeting Buchanan 100

Monday, May 22

07:30-8:30 Continental Breakfast Buchanan Lobby

08:00-17:00 Registration available

SPEAKERS: **note to all speakers: Please go to the lecture hall one half hour before your talk to load your talk on the computer and ensure that everything is working**

08:30-10:30 **Symposium IV: Recent perspectives on the role of monoamine systems in depression**; Chairs: F. Scott Hall and Andrew Holmes

F. Scott Hall - Molecular Neurobiology Branch, National Institute on Drug Abuse, NIH, USA - *Antidepressant-like effects of DAT or NET, but not SERT, gene knockout on behavior in the forced swim test*

Tim Newman - Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, NIH, USA - *Rhesus macaque homologues of human polymorphic alleles of monoaminergic genes*

Steven A. Thomas **-** University of Pennsylvania, Philadelphia, Pennsylvania, USA - *Norepinephrine-deficient mice lack responses to antidepressant drugs, including selective serotonin reuptake inhibitors*

Klaus Peter Lesch - University of Wuerzburg, Germany - *Gene-environment interaction in emotion regulation*

10:30-10:45 Symposium IV Discussion

10:45-11:15 Coffee Break

11:15-12:00 **Plenary Address by Young Scientist Award recipient** Dr. Andrew Holmes, National Institute on Alcohol Abuse and Alcoholism, NIH, USA, **"The Ascent of Mouse: using mice to understand the causes and cures of neuropsychiatric disease"**

12:00-13:30 Lunch

13:30-14:45 **Invited Talks – *Outstanding Young Investigators*** Chair: Catharine

Rankin

Viviane Labrie – Mt. Sinai Hospital Hospital and University of Toronto, Ontario, Canada – *Decreased glycine affinity at the NMDA receptor results in impaired switching behaviors in mice that are reversed by D-Serine*

Christine Ponder – Columbia University, New York, USA - *Short-term selected lines for fear conditioning: QTL and gene expression analysis*

Yann Mineur – Yale University, New Haven, Connecticut USA - *Localized expression of Beta2-containing nicotinic acetylcholine receptors in dopaminergic neurons in mice supports locomotor activating, but not rewarding effects of nicotine*

Heather Haughey – University of Colorado at Boulder, USA - *The human $GABA_A$ Receptor $\alpha 2$ Gene (GABRA2): findings from an alcohol endophenotype study and post-mortem brain expression anaylses*

14:45-15:00 Break

15:00-17:00 **Symposium V: Ethological and genetic analysis of social behaviour**; Chairs: Enrico Alleva and Robert Gerlai

Enrico Alleva - Istituto Superiore di Sanità, Rome, Italy - *Effects of early social enrichment on adult mouse social phenotype*

Hewlet McFarlane - National Institute of Mental Health, NIH, USA – *Social play in C57BL/6J and BTBR T^+ tf/J mice*

James Curley - University of Cambridge, United Kingdom - *The role of the maternal environment on the development of alternative behavioural phenotypes in mice*

Robert Gerlai - University of Toronto, Ontario, Canada – *Social behaviour of zebrafish: A target of mutagenesis?*

17:15-17:30 Symposium V Discussion

17:30-18:00 Closing Remarks

18:00-19:00 BREAK

18:30 cash bar opens Student Union Building (SUB) party room

19:00 –22:00 Closing Banquet

ABSTRACTS

PRESIDENTIAL PLENARY LECTURE

MOLECULAR, CELLULAR, AND CIRCUIT MECHANISMS UNDERLYING HIPPOCAMPAL MEMORY
SUSUMU TONEGAWA

We study molecular, cellular, and neuronal circuit mechanisms underlying acquisition, consolidation and retrieval of hippocampus-dependent memory in rodents. Our primary approach is to generate cell type and adult-restricted knockout mice and characterize them using multifaceted methods including molecular and cellular biology, *in vitro* and *in vivo* electrophysiology, conforcal and two photon microscopy and behavioral tasks. The data obtained to date indicate that NMDA receptor-mediated synaptic plasticity in area CA1 plays a pivotal role in special and other hippocampus dependent learning and memory. The same receptors and synaptic plasticity in area CA3 is dispensable for the acquisition of reference memory, but plays an important role in "pattern completion"-based memory recall as well as in a rapid , one trial-based learning. NMDA receptor function in detate gyrus (DG) is also dispensable for reference memory, but is important in "pattern separation." These studies attest the power of this multi-faceted approach in identifying mechanisms underlying cognition.

The Picower Institute for Learning and Memory, RIKEN-MIT Neuroscience Research Center, Howard Hughes Medical Institute, Department of Biology and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, USA.

SYMPOSIUM I: "FROM MOUSE GENETICS TO GENOMICS TO BEHAVIOR: 35 YEARS OF PROGRESS. A SYMPOSIUM TO HONOR THE WINNER OF THE 2005 IBANGS DISTINGUISHED SCIENTIST AWARD, DR. LARRAINE FLAHERTY," ORGANIZED BY DOUGLAS WAHLSTEN

COMMON THEMES FROM MY 30 YEARS WITH LORI FLAHERTY
G RINCHIK

I had the distinct privilege and pleasure of a 30-year association with Dr. Lori Flaherty, an association that, over time, encompassed many types of relationships ranging from mentor, advisor, collaborator, go-to friend, and colleague. From my vantage point over those years, several common themes in Lori's career became readily apparent. Some of these themes related to Lori's approach to science and to using common and often slightly misunderstood "mouse reagents" in new ways. In this context, I will provide a glimpse into her early days of her research group (1975-1980) to provide one example of how an approach she used in immunogenetics over 30 years ago could be re-applied to her new-found, later-blooming interest in behavioral neurogenetics. Other themes were more general, and of the type that are instructive for excelling in science, for helping others excel too, and for having a good time while doing so. All aspects of her career were valuable to evaluate and to learn from.

Genetics, Taconic Farms, Inc, Hudson, New York USA.

DISSECTING BEHAVIOR: THE POWER OF MOUSE GENETICS
V BOLIVAR

Genetically defined mouse strains (e.g., inbreds, congenics, RI lines, knockouts, transgenics) have become invaluable research tools for evaluating the underlying genetics and cell biology that translate into behavioral phenotypes. Perhaps no one appreciated the significance of genetically defined mouse strains more than Lori Flaherty. She firmly believed that as a model system, the mouse was ideal for the study of many complex traits, including behavior. Almost nine years ago she asked me – an experimental psychologist - to join her molecular genetics laboratory at Wadsworth Center as a postdoctoral fellow. Her philosophy was simple – you teach me behavior and I will teach you genetics. Although over the years my role at Wadsworth changed from postdoctoral fellow to independent researcher, we continued to "teach each other" until her untimely death in February. Together we used genetically defined strains to search for

genes involved in complex behaviors (e.g., exploratory behavior, fear conditioning). By analyzing crosses between inbred lines of mice that differed in behavioral performance, we were able to establish genetic loci (regions) correlating with these behaviors. For instance, we established loci on Chromosomes 1 and 15 involved in exploratory behavior and a locus on Chromosome 1 involved in contextual fear conditioning. We are currently evaluating candidate genes from these regions. The ultimate goal of this research is to understand the neural pathways involved in these complex behaviors, and we believe that this genetic methodology, in combination with other behavioral neuroscience techniques, will provide confirmatory evidence for known pathways and help uncover new ones.
Genomics Institute, Wadsworth Center, New York State Department of Health, Troy, New York USA. This work was supported by NIMH.

OF MICE AND LORI: SIMPLE LESSONS IN GENETICS, FRIENDSHIP AND COURAGE
M COOK

I joined Lori's lab at the end of 1998 after an initial post-doc in France where I began to learn molecular genetics. Because of my interest in learning more about genetics, Lori's expertise in this area, and her quest to learn more about mouse behavior, Lori's lab was the perfect setting to continue my learning. By the late 1990's, the almost exponential growth in the number of knockout and transgenic mouse models presented the possibility of characterizing the role(s) of many different genes in a myriad of phenotypes. As a post-doc in Lori's lab and after the compilation of an extensive review of reported knockout and transgenic phenotypes, the contradictions in reported phenotypes for the same genes became evident. Those contradictions were largely based on differences in genetic backgrounds upon which the knockout and transgenic animals were created. Further inspection led us to realize that surprisingly little had been done to extensively phenotype the parental strains. So, we set out to simply characterize commonly used inbred strains in a variety of tasks. Not so surprisingly, our findings indicated the importance of background strain consideration in the interpretation of data obtained from knockout and transgenic animals. The foundations of my current research are rooted in experiences with Lori. I can only hope that, through my work, I can contribute a fraction of what she contributed to the scientific community. I am proud to have had Lori as a mentor and even prouder to have had her as a friend.
University of Memphis, Tennessee, USA.

X CHROMOSOME CONTROL OF CORPUS CALLOSUM FORMATION
GK KUSEK[1,2], D WAHLSTEN[3], BJ HERRON[1,2], VJ BOLIVAR[1,2], L FLAHERTY[1,2]

Corpus callosum size in mice is a complex quantitative trait that is influenced by interactions between multiple genes and environmental effects. For example, the corpus callosum is completely absent in BTBR T/+ tf/tf (BTBR), while BALB/cByJ (BALB) show variable corpus callosum size. Identification of genes that influence corpus callosum formation in mice will lead to better understanding of the mechanisms controlling development of this structure. Previous work has implicated genes on the X chromosome in corpus callosum development. We performed reciprocal crosses between BTBR and BALB to investigate this possibility. We found that the X chromosome derived from BTBR possesses dominant alleles resulting in a decrease in the mean midsagittal area of the corpus callosum. A backcross subsequently identified two QTLs on the X chromosome that influence corpus callosum size, one at 68.5Mb and the other at 134.5Mb (NCBI Build 34). Global gene expression analyses on total RNA from embryonic day 16.5 brains of reciprocal F1 male mice revealed gene expression differences that are influenced by the X chromosome. Differentially expressed genes within our critical intervals are currently being examined as candidate genes contributing to agenesis of the corpus callosum in BTBR inbred mice.
[1]Genomics Institute, [2]Department of Biomedical Sciences, University at Albany, State University of New York, New York USA. [3]Department of Biological Sciences and Great Lakes Institute, University of Windsor, Windsor, Ontario CANADA.

PAPER SESSION

ENVIRONMENTAL ENRICHMENT REDUCES Aβ DEPOSITION IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE: INVOLVEMENT OF MULTIPLE PROCESSES

O AMBR I E[1,2], N G_RTZ[2], A HERRING[1], N SACHSER[2], W PAULUS[1], K KEYVANI[1]

Alzheimer's disease (AD) is the most common form of senile dementia worldwide. Epidemiological studies suggest that the diversity and intensity of premorbid intellectual and physical activities inversely correlate with onset and development of AD. The aim of this study was to model different "lifestyles" in a transgenic mouse model of AD by keeping the animals in different housing conditions and to discover underlying mechanisms of thereby evoked effects. Female mice from the TgCRND8 line carrying human $APP_{Swe+Ind}$ were housed either in standard or in enriched housing condition from 30 days until 5 months of age. The immunohistochemical detection of Aβ revealed that Aβ plaques as well as amyloid angiopathy were significantly reduced in EH mice. Neither human APP transgene expression levels as measured by TaqMan assay nor soluble Aβ content as measured by ELISA differed between both groups. DNA microarray analysis revealed simultaneous downregulation of pro-inflammatory genes as well as upregulation of molecules involved in anti-inflammatory processes, proteasomal degradation, and cholesterol binding possibly involved in the reduction of Aβ burden. Additionally, elevated microgliosis in the "enriched" brains were found, as shown by immunoblotting against F4/80 antigen. In summary, a reduction of Aβ deposition can be obtained by continuous and diversified environmental stimulation. Multiple processes seem to be involved in Aβ burden reduction by lower aggregation and enhanced clearance of Aβ.

[1]Institute of Neuropathology, [2]Department of Behavioural Biology, University of Münster, Münster, Westphalia, GERMANY. This work was supported by a grant from "Innovative Medical Research" (IMF KE520401).

THE MOLECULAR SWITCH OF THALAMIC SENSORY GATING

E CHEONG, S LEE, J CHOI, M SUN, CJ LEE, H-S SHIN

Thalamus has a critical role in sensory gating, relaying various sensory signals received from spinal cord to cortex. Thalamic relay neurons produce two different patterns of electrogenic activity; tonic series of single action potentials that acts as an open gate, a faithful relay mode, and rhythmic bursts of spikes that work as a closed gate, an inhibitory mode. In recent studies, rhythmic burst firing in thalamic relay neurons was shown to require an activation of the low-voltage-activated α1G T-type Ca^{2+} channels. However, there have been debates on how the transition between burst and tonic firing occurs and how two firing modes are modulated. We have investigated the modulation of firing pattern of thalamic relay neurons using PLCβ4 deficient mice which exhibits diminished pain responses. Here we show that activity of mGluR1-PLCβ4 pathway concomitantly controls burst and tonic firings of thalamic relay neurons. This is evidenced by an increase in burst firing and a decrease in tonic firing of the PLCβ4 (-/-) thalamic relay neurons, which results from a concomitant increase in T-type and L-type Ca^{2+} channel currents. In PLCβ4 (-/-), an increase in T-type Ca^{2+} currents augments burst firing, whereas an increase in L-type Ca^{2+} currents decreases tonic firing by increasing Ca^{2+} influx, which subsequently increases the contribution of after-hyperpolarization mediated by Ca^{2+} activated channels. Our study proposes that the mGluR1-PLCβ4 pathway in thalamic relay neurons serves as a "molecular switch" to set the state of the thalamic relay neurons, open-gate versus closed-gate.

Center for Neural Science, Division of life sciences, Korea Institute of Science & Technology, Seoul KOREA. This work was supported by the Chemoinformatics Program of the Korea Institute of Science & Technology (Grant No. 2E18790).

GENETICS AND GENOMICS OF BIPOLAR DISORDER: COMBINING MULTIPLE DATA TYPES AND GENERATING MEANING FROM THE MANIA

P STAFFORD, F CASIDY, JC BADGER, C ZHAO, S ROCHE, PJ MCKEON, SE DOBRIN

Bipolar disorder (BPD) is a severe and debilitating psychiatric illness with a proven genetic component, but the genes involved in the disorder have yet to be fully elucidated. Genome-wide linkage scans of BPD have identified several putative susceptibility loci, including 4p16, 6pter-p24, 10q25-26, 12q23-24, 13q31-32, 18p11, 18q21-23, 21q22 and 22q11-13. Meta-analysis provides additional support for 13q and 12q as BPD susceptibility loci. Several gene expression studies have resulted in mixed results supporting various hypotheses about BPAD etiology. Here we present the overlaying of two BPAD datasets, a 10 cM genome scan and a whole-genome expression study. A 10cM scan, employing a panel of 402 microsatellite markers, was performed on a collection of 60 Irish bipolar affected sib pair (ASP) families. Pair-wise and multipoint, non-parametric linkage (NPL) analysis was performed using Allegro and GeneHunter Plus. Genome wide association testing was performed using ETDT. Expression studies were performed from RNA extracted from the prefrontal cortex of 35 BPAD and 35 unaffected individuals. Initial analysis was performed using ANOVA and gene lists generated from those gene producing a $P<0.01$. The physical map from the genome scan and the known positions from the expression study were aligned. Here we present the first instance of overlapping TDT and NPL scores of major significance in the same BPD cohort. Peak NPL and TDT P-values < 0.01 are observed at the same region in most and the same marker in three of the peaks. Using this method we are able to make better use of both the expression data and the linkage data in piecing together the molecular etiology of this complex disease.

Center for Medical Genetics, Marshfield Clinic, Marshfield, Wisconsin USA.

DIFFERENCES IN GENETIC ORIGINS AND ATTENTIONAL RESPONSES BETWEEN PURE AND COMORBID ANXIETY DISORDERS IN HUMANS

M-A ENOCH, KV WHITE, J WAHEED, X-Z HU, CR HARRIS, D GOLDMAN

Anxiety disorders are common diseases that are often comorbid with major depression (MD) and alcohol use disorders (AUD). Recent MRI and FMRI studies have detected differing relationships between the neurocircuitry of emotion / fear and three common, functional polymorphisms: the serotonin transporter promoter polymorphism HTTLPR, catechol-O-methyltransferase (COMT) Val158Met and brain-derived neurotrophic factor (BDNF) Val66Met. We hypothesized that there would be genotype and neurobiological differences, measured as attentional response (auditory P300 event related potential) and working memory (WAIS-R digit symbol (DS)), between pure anxiety disorders and comorbid anxiety. Our study sample comprised 249 community-ascertained men (n = 108) and women (n = 141) with lifetime DSM-III-R diagnoses. We compared five groups of participants with: single diagnoses of anxiety, MD or AUD, comorbid anxiety and no psychiatric disorder. Individuals with pure anxiety disorders had elevated auditory P300 amplitudes ($p = 0.0004$), higher WAIS-R DS scores ($p < 0.0001$) and the highest frequency of the HTTLPR S allele ($p = 0.08$) compared with all the other groups. Individuals with comorbid anxiety had the greatest proportion of COMT and BDNF Met alleles ($p = 0.009$) as well as higher harm avoidance / neuroticism ($p < 0.0005$) than all other groups. Our results suggest that there may be two vulnerability factors for anxiety disorders with differing genetic susceptibility: (a) heightened attentional responses, better working memory and mildly elevated anxiety/neuroticism that may be protective against other psychopathology, and (b) poorer attentional responses / working memory and greater anxiety/neuroticism; vulnerability factors for AUD and MD. This refinement of the anxiety phenotype may have implications for animal models and for therapeutic interventions.

Laboratory of Neurogenetics, NIAAA, NIH, Bethesda, Maryland 20892 USA.

BEHAVIORAL, PHARMACOLOGICAL, AND GENE EXPRESSION DIFFERENCES BETWEEN LINES OF MICE BRED FOR DIFFERENCES IN EXPLORATORY BEHAVIOR

CL KLIETHERMES, JC CRABBE

We have recently selectively bred rodents for divergent expression of head dipping behavior on the hole-board apparatus, resulting in replicate lines of mice that show High or Low Exploratory Behavior (HEB and LEB mice, respectively). These lines of mice possess distinct allelic combinations associated with

divergent exploratory behavior, which has been proposed as a behavior relevant to human novelty seeking tendencies. To determine whether artificial selection may have altered genes relevant to drug reward, we compared HEB and LEB mice for ethanol and d-amphetamine conditioned place preference (CPP). No differences between HEB and LEB mice were found for CPP resulting from either drug. In a separate experiment, HEB mice of both replicates showed markedly higher methamphetamine-induced stimulation compared with LEB mice, but the selected lines did not differ in response to diazepam. Finally, we compared basal gene expression profiles in hippocampi of HEB and LEB mice using the criterion that a given transcript had to be significantly different between HEB and LEB mice of both replicates at $p < 0.05$. Most of the 50 genes identified showed higher expression in HEB mice and had known or inferred roles in the regulation of transcription and/or cell differentiation. This raises the possibility that compared with LEB mice, HEB mice may have higher rates of neurogenesis, and that this might function in some of the differences between the selected lines.

[1]Department of Behavioral Neuroscience, Oregon Health & Science University, Portland Oregon USA; Current position: Ernest Gallo Clinic & Research Center, University of California-San Francisco, Emeryville, California USA. [2]Portland Alcohol Research Center, Department of Behavioral Neuroscience, Oregon Health & Science University, and VA Medical Center, Portland Oregon USA. Supported by NIH-NIAAA Center Grant AA10760, and the US Department of Veterans Affairs.

LARGE SCALE GENE EXPRESSION ANALYSIS IN THE HYPOTHALAMUS OF AN ANIMAL MODEL OF DEPRESSION

DH SEGAL[1], KR WALDER[1,2], M MALAKELLIS[1], AJ SANIGORSKI[1], GR COLLIER[1,2]

We have developed social isolation of the Israeli sand rat (*Psammomys obesus*) as a possible animal model of depression and used cDNA microarray analysis to identify differentially expressed hypothalamic genes that may play a role in the onset and resolution of depression-like behaviour. Socially isolated animals spent significantly less time in the inner region of the OFT apparatus compared with communally housed controls (15.9±1.5 seconds vs 21.8±1.8 seconds, p=0.01). In addition, socially isolated animals spent more time immobile in the FST compared with communally housed controls (137±6 seconds vs 113±8 seconds, p=0.03). These findings are consistent with social isolation of *P. obesus* being a model of depression. In a second experiment, animals were socially isolated for 2, 4, 6 or 8 days and hypothalamic RNA was extracted and hybridised to a custom-made *P. obesus* cDNA microarray. Microarray analysis of hypothalamic gene expression identified over 100 genes as showing evidence of being differentially expressed between separated and unseparated animals. Examples of candidate depression genes that exhibit increased expression following social isolation include angiotensinogen (p=0.001) and Na^+K^+ ATPase1□2 (p=0.01). Intracerebroventricular administration of Na^+K^+ ATPase1□2 antisense oligonucleotides into the brain of *P. obesus* was shown to significantly increase time spent in the inner region of the OFT (p=0.01). These findings suggest that Na^+K^+ ATPase1□2 may play a significant role in modulating behaviour. Studies are ongoing to further validate social isolation of *P. obesus* as a new animal model of depression.

[1]Metabolic Research Unit, School of Health Sciences, Deakin University, Waurn Ponds AUSTRALIA, [2]ChemGenex Pharmaceuticals, Geelong AUSTRALIA. This work was supported by ChemGenex Pharmaceuticals.

A NEUROETHOLOGICAL APPROACH TO DISSECTING THE ROLES OF CEREBELLAR PURKINJIE CELLS IN OPEN FIELD BEHAVIOR

SWANSON[1], E BRAUER[1], G RAMIREZ[2], M BUTLER[1], E POLOSETSKY[3], Y BENJAMINI[4], I GOLANI[3], D GOLDOWITZ[1]

Behavioral deficits in some human syndromes such as Autism have been associated with cerebellar deficits. The cerebellum has also received attention for its involvement in cognitive behaviors, such as spatial navigation and working memory. Animal models with genetic lesions that affect cerebellar function display graded levels of ataxia dependent on the severity and specific cerebellar cell types involved. We have combined the use of experimental chimeras of the cerebellar ataxic *lurcher* (*Lc/+*) mutant with a robust and highly reproducible open field behavior analysis approach (SEE, software supported Strategy

for the Exploration of Exploration) to determine the influence of cerebellar Purkinje cell deficits on motor and cognitive behaviors. Lurcher chimeras (with various proportions of *Lc/+* and wildtype cells) provide a useful animal model in which we can generate mice with varying degrees of Purkinje cell degeneration, due to the cell autonomous apoptosis of Purkinje cells containing the *lurcher*-GRID2 mutation. SEE provides an analysis of natural behaviors in a two-meter open field arena, yielding a multitude of novel, ethologically relevant behavioral endpoints that distinguish motor and cognitive phenotypes. Using the basic SEE-workshop analyses we show that 17 out of 36 endpoints were significantly different between ataxic-*Lc/+* and normal-*+/+* mice, and two endpoints, MSDR (akin to acceleration) and LMS (velocity of body movement during pauses), can completely distinguish ataxic and normal mice. These quantitative endpoints serve as baseline for subsequent dissection of behavioral deficits in Lc/+←→+/+ chimeras. Our analysis demonstrates that the overt ataxic phenotype of the Lurcher mutant can be overcome in chimeras by as few as 5% of the normal compliment of +/+ Purkinje cells. While most chimeras with < 6000 or >20000 Purkinje cells are behaviorally indistinguishable from Lc/+ or +/+ mice respectively, there are several chimeras that exhibit mixed SEE endpoint classifications (wildtype-like and mutant-like). These chimeras have a lower threshold of Purkinje cells and thus may represent an intermediate phenotype that may be associated with Purkinje cell number or connectivity.

[1]University of Tennessee Health Sciences Center, Memphis, Tennessee USA.
[2]Chaminade University, Honolulu, Hawaii USA.
[3]Department of Zoology, [4]Department of Statistics, Tel Aviv University, Tel Aviv ISRAEL. This work was supported by NIH grants R25-MH066890 and R01-MH074460.

THE EFECTS OF STIMULATION AND ETHANOL EXPOSURE ON LONG-TERM MEMORY TRAINING IN *C. elegans*

M BUTTERFIELD[2,3], C RANKIN[1,3]

Ethanol has been shown to have inhibitory effects on memory in many mammalian systems. Previously, our lab has demonstrated, using a distributed training protocol, that *C. elegans* is capable of long-term memory for habituation (>24 hours). The current studies examined whether ethanol exposure would affect long-term memory by exposing worms to various concentrations of ethanol (0.2M, 0.4M and 0.6M; as originally described in Davies *et al*. 2003) during training. Worms that were given habituation training 24 hours earlier without ethanol (0.0M) showed significantly smaller responses than the control group that did not receive any habituation training ($p<0.0001$), indicating long-term memory. Worms trained on 0.2M ($p=0.1787$) and 0.4M ($p=0.7235$) ethanol showed no significant difference in responses between control and trained suggesting that ethanol exposure may interfere with memory formation. Since other researchers have shown that some mutant strains of *C. elegans* show altered behavioral responses to ethanol, it is our hypothesis that one or more of these genes may be critical to rescuing the memory deficit that we have identified. Davies *et al.* (2004) has shown that alteration in the functional level of NPR-1 (a homologue of a neuropeptide y receptor) may be a mechanism for acute ethanol tolerance in *C. elegans.* We administered our training protocol to the *npr-1* mutants in both the absence (0.0M) and presence (0.4M) of ethanol. When tested 24 hrs later, the ethanol exposed group showed no significant difference in response ($p=0.4811$) while the group without ethanol exposure showed significantly smaller responses in the trained animals as compared to the control animals ($p<0.05$) indicating that this gene may not rescue the memory deficit. Davies, *et al.* (2003) has also shown that when *slo-1* mutants are exposed to ethanol the majority of behavioral deficits are abolished. Therefore, we are currently testing these mutants for long-term memory for habituation.

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DISTINGUISHED SCIENTIST AWARD PLENARY LECTURE

GENETIC HERITABILITY: AN OLD BOTTLE FOR SOME 21ST CENTURY WINE

DOUGLAS WAHLSTEN

The term "heritability" is used in two ways in neurobehavioral genetics, (a) as a generic indicator of parent-offspring similarity or transmissibility, and (b) as ratio of genetic to phenotypic variance based on a purported partition of genetic (G) and environmental (E) causes of individual differences. Partitioning variance is valid only when the factors are additive (G + E), but we know from many studies of development and the environmental control of gene expression that additivity is biologically bogus. In research with animals, inbred strain comparisons or selective breeding are often used to assess heritability. These methods are sensitive to the maternal environment, indirect genetic effects, mitochondrial genes and other non-mendelian influences, including in some cases "cultural inheritance." Along with chromosomal genes, these multifarious causes of parent-offspring resemblance comprise the individual's more broadly construed heredity (H). Either the field must give up the use of "heritability" as a genetic parameter because there is no generally valid way to separate the influences of G versus E, or it must change the definition of heredity to be a more inclusive H rather than strictly mendelian G and regard "heritability" as a generic statistical indicator.

Great Lakes Institute for Environmental Research, Department of Biological Sciences, University of Windsor, Ontario CANADA.

SYMPOSIUM II: "EMOTION, PLAY, AND DOMINANCE,"

THRESHOLD OF CONSCIOUSNESS IN PHYLOGENY

M CABANAC

Anatomy and dopamine content of the brain suggest a functional difference between amphibians and reptiles. The absence of emotional tachycardia and fever in frogs, suggests that emotion emerged in the evolutionary lineage between amphibians and reptiles. Acquired taste aversion is present in reptiles but not in amphibians. These results would imply that reptiles, and more recent vertebrates, possess consciousness with its characteristic hedonic dimension, pleasure, that optimizes behavior. The existence and role of sensory pleasure in decision making were also verified in lizards placed in a motivational conflict: pleasurable tastes vs. cold ambient temperature. Arguments drawn from the structure of sleep and the presence of play behavior would confirm that a qualitative step took place between amphibians and reptiles. It is proposed, therefore, that consciousness likely emerged in the reptilian common ancestors of nowadays reptiles, birds, and mammals.

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THE ORIGINS OF VERTEBRATE PLAY: A ROLE FOR THE HERITABILITY OF EXPERIENCE

GM BURGHARDT

Play behavior is a common and robust phenomenon in many mammals and birds, but it has proven difficult to characterize play sufficiently to be able to identify comparable behavior in other vertebrate classes. Various approaches emphasize behavioral, emotional, neural, developmental, experiential, and functional properties of play. A set of criteria accommodating such attributes has been formulated that leads to recognizing putative play in fishes, amphibians, and non-avian reptiles. Characterizing commonalities of play among vertebrates supports a theoretical framework, Surplus Resource Theory, that suggests how play originated and diversified to reach its most diverse and complex forms in endothermic vertebrates with large and complex brains. While earlier authors argued that play is a distinctive and discontinuous property of the most intelligent animals, new data establish that play, while not homologous across all vertebrates, is widely distributed and mediated by brain regions controlling 'instinctive' behavior. The genetic underpinnings of play may involve threshold effects and developmental shifts in the heritability of behavior and perception. Data will be presented on heritability of experience in

garter snakes showing that such mechanisms underlying behavioral plasticity both can be demonstrated and provide a plausible mechanism underlying the genesis of playfulness and novel behavior in general.
Departments of Psychology and Ecology & Evolutionary Biology, University of Tennessee, Knoxville, Tennessee USA.

MOTIVATIONS FOR SOCIAL APPROACH BEHAVIORS AMONG JUVENILE *Mus musculus*
G LAHVIS
Social interaction among mammals, from large groups to dyads, requires social approach. Among adults, social groupings, such as monogamous pair-bonds and maternal attachments to infants are strongly influenced by nonapeptides, such as oxytocin and reproductive hormones. Much less is known about the neurobiology of peer groupings among adolescent animals. Adolescent social interactions can be less selective, more playful, and less directly related to reproductive success than interactions among adults. Given the breadth of genetic approaches available for mice, we ask here whether adolescent mice are motivated for social approach and whether these approach behaviors are influenced by genetic background. We find that approach towards social interactions and their associated environmental cues among adolescent animals can be very strong, suggesting that the subjective experience of reward may underlie motivations for peer interactions. In this regard, mouse strains show different degrees of social approach during adolescence; patterns that are lost with the emergence of gender-specific sociality. These observations are consistent with studies of others on opioid systems in juvenile social play, but may also suggest genetic factors that exert a unique influence on adolescent social reward. Genetic influences on juvenile social approach will be considered within the contexts of evolutionary theory and social neuroscience.
Department of Surgery, University of Wisconsin – Madison, USA.

ULTRASONIC VOCALIZATIONS AS INDICES OF AFFECTIVE STATES IN RATS AND ASSOCIATED GENETIC CONSEQUENCES
JAAK PANKSEPP
The nature of affective processes in the brain is rapidly becoming a key topic in behavioral neuroscience as well as cognitive neuroscience. One current view is that there are many varieties of affect (emotional, homeostatic, and sensory), and one emerging view is that emotional affects are elaborated by the same brain operating systems that generate emotional-instinctual behaviors, perhaps best indexed by emotional vocalizations. 55 kHz Ultrasonic vocalizations (USVs) are especially evident during social-interactions and appetitive states. Converging evidence indicates 55 kHz USVs reflect positive affective states, a response most evident during social play which can be maximized with heterospecific human hand play (i.e., "tickling"). The circuitry is associated with ascending brain dopamine "reward" circuitry. 22 kHz USVs index a negative emotional state that is commonly evoked by fearful threats and competitive social defeat. Animals that have been selectively bred for high tickle-induced 55 kHz USVs, also exhibit low-levels of 22 kHz USVs, while those selected for low 50 kHz USVs exhibit high levels of 22 kHz USVs during tickling. Juvenile play is characterized by abundant 50 kHz USVs compared to adult intermale fighting, where 22 kHz USVs prevail. Preliminary data summarizing differential microarray estimated gene-expression patterns resulting from these two dynamic social interactions will be summarized.
Department of VCAPP, College of Veterinary Medicine, Washington State University, Pullman, USA.

<u>SYMPOSIUM III</u>: "MOUSE SENSORY SYSTEMS AND BEHAVIOUR," CHAIRED BY RICHARD BROWN

THE INFLUENCE OF VISUAL ABILITY ON THE BEHAVIOR OF MICE IN A BATTERY OF TESTS
AA WONG, RE BROWN
We evaluated visual detection, pattern discrimination and visual acuity in 13 strains of mice at 3 months of age. Mice with no known visual defects (129SI/Sv, C57BL/6J and DBA/2J) performed well on all three

visual tasks; mice with poor vision due to photoreceptor damage (AKR/J, BALB/CbyJ) showed moderate improvement and mice with retinal degeneration and other visual defects (A/J, C3H/HeJ, CAST/Ei, FVB/NJ, MOLF/Ei, SJL/J, SM/J and SPRET/Ei) performed at chance levels. These and other mice of the same strains were tested in a behavioral test battery that evaluated anxiety-related behavior, motor performance and learning and memory. Strain differences in visual acuity accounted for a significant proportion of the variance in tasks dependent on visual cues. Although DBA/2J mice have normal vision at 3 months of age, between 9 -12 months of age they develop a condition that resembles age-related pigmentary glaucoma in humans. Changes in visual ability, learning and memory were evaluated in DBA/2J, C57BL/6J, B6.mpc1d and D2.mpc1b mice at 6, 12, 18 and 24 months of age. At 6 months, DBA/2J and D2.mpc1b mice (a D2 congenic strain) outperformed C57BL/6J and B6.mpc1d mice (a C57 congenic strain) in the visual detection task and there were no strain differences in performance on the Morris water maze. At 12, 18 and 24 months, C57BL/6J and B6.mpc1d mice outperformed DBA/2J and D2.mpc1b in the vision tasks and in the water maze. Strains did not differ in the olfactory learning task. Strain differences in visual task performance accounted for a significant proportion of the variance in measures of learning and memory in the water maze at 12, 18 and 24 months of age. These results indicate that visual ability must be accounted for when testing for strain differences in mice because differences in performance in many tasks may be due to visual deficits rather than differences in higher order cognitive functions.
Psychology Department & Neuroscience Institute, Dalhousie University, Halifax, Nova Scotia CANADA.
Supported by JAX Phenome project and NSERC of Canada.

OLFACTION AND MOUSE BEHAVIOUR
HM SCHELLINCK, RE BROWN
Odour cues dominate the life of the mice. Even prenatal or perinatal exposure to odorants can affect later postnatal behaviour and infant mice are easily conditioned to approach or avoid odours. As adults, mice communicate largely through odours and may discriminate between individuals based upon their sex, age, territory and dominance status. In addition, exposure to the odour of conspecifics may create dramatic changes in behaviour and reproductive status. This reliance upon odour stimuli creates an ideal context for the examination of learning and memory processes using olfactory based paradigms. In this presentation, we will discuss the advantages and disadvantages of different methodologies and some of the most current findings in the area of olfaction and behaviour in mice.
Psychology Department, Dalhousie University, Halifax, Nova Scotia CANADA. Supported by NSERC of Canada grants to HS and REB.

HEARING AND MOUSE BEHAVIOR
SL MCFADDEN[1], JF WILLOTT[2]
For decades, several strains of inbred mice have served as models of human presbycusis, or age-related hearing loss (ARHL), because they exhibit consistent, well-defined patterns of progressive hearing loss as they age and a pattern of cochlear degeneration similar to that seen in many aging humans. More recently, inbred and mutant strains of mice have become popular as models for understanding the genetic and biochemical mechanisms underlying noise-induced hearing loss (NIHL) and drug-induced hearing loss (DIHL) as well. In this talk, we will describe the basic hearing capabilities of mice and how genetic background and hearing loss can influence performance in tasks involving auditory stimuli, such as the acoustic startle response (ASR) and prepulse inhibition (PPI). The auditory capabilities of a strain should be taken into consideration when designing studies that include tasks that rely on auditory performance, and when comparing performance among mice with different genetic backgrounds.
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TASTE AND BEHAVIOR IN MICE

AA BACHMONOV

The taste perception is involved in several types of behaviors. The most direct link is with the ingestive behavior: palatability or aversiveness of taste determines food choice and consumption. In a similar fashion, the taste perception also affects oral self-administration of drugs, e.g., ethanol, morphine or nicotine. Taste stimuli are used as conditioned or unconditioned stimuli in experiments involving learning. These behavioral studies often involve mouse strains that differ in taste responses, which can affect results of behavioral experiments. We have examined preferences for sweet, bitter, salty, sour and umami-tasting solutions in 28 inbred mouse strains and have found a large variation in responses to most of the taste stimuli. This variation in taste responsiveness must be taken into account when experiments involving taste stimuli are designed.

Monell Chemical Senses Center, Philadelphia, Pennsylvania 19104 USA. This work was supported by NIH grants AA011028, DC00882 and DC03854.

GENETIC VARIABILITY AND CONSIDERATIONS FOR PAIN MEASUREMENT IN INBRED AND TRANSGENIC MICE

SB SMITH[1,2], JS MOGIL[1,2]

Mouse strains exhibit tremendous variability in their responses to nociceptive stimuli. Likewise, sex and genotype play significant roles in determining sensitivity to analgesic drugs. A growing appreciation of these genetic differences has contributed to our understanding of pain modulation, and we have uncovered quantitative trait loci contributing to variability for a number of pain modalities. Our findings bear relevance to the investigation of knockout and transgenic phenotypes, as the background strain on which the mutation is placed can introduce confounding issues. The default strains used for knockout construction, 129 and C57BL/6, display atypically extreme behaviors on the majority of common pain tests, which should be taken into account when designing experiments. Such strain differences, while a potential source of confounds, may also be exploited to reveal genetic factors underlying interindividual pain variation by using knockout mice as *ad hoc* congenic strains. We are also beginning to explore the role of other senses in affecting pain response in mice. Data will be presented showing that pain experience may be communicated between mice, but only if the appropriate sensory modalities are preserved.

[1]Department of Psychology and [2]Centre for Research on Pain, McGill University, Montreal, Quebec, CANADA. This work was supported by a CIHR Strategic Training Fellowship in Pain: Molecules to Community (SBS) and the U.S. National Institutes of Health (JSM).

VIBRISSA FUNCTION AND SOMATOSENSORY CORTEX PLASTICITY IN MICE

RH DYCK[1,2], AE BAXTER[1], CE BROWN[1]

Our research seeks to determine the mechanisms of experience- and activity-dependent plasticity in the mammalian cerebral cortex using, as our model, vibrissa mediated somatosensation. Sensory information provided by the vibrissae mystaciales is essential for the survival of murine species. Removal of these mobile tactile sensors leads to deficits in tactile discrimination, orientation, locomotion, and balance. The advantage of this studying this sensory modality in the laboratory is related to the fact that input from each vibrissa is represented in primary somatosensory cortex within a distinct morphologically- and functionally-defined compartment. We have assessed somatosensory cortex plasticity, using behavioural and anatomical methods, in wild type, transgenic and knockout mice, in order to gain an understanding of the molecular requirements for cortical plasticity. Here we will describe recent anatomical and behavioural studies that we have undertaken in mice that have had the gene for monoamine oxidase A genetically silenced. The resultant, developmentally transient increase in serotonin levels in the cerebral cortex prevents the formation of the morphological compartments innervated by vibrissa-specific inputs and has significant consequences for synaptic plasticity and vibrissa-dependent behaviours.

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SYMPOSIUM IV: "RECENT PERSPECTIVES ON THE ROLE OF MONOAMINE SYSTEMS IN DEPRESSION," CHAIRED BY F. SCOTT HALL AND ANDREW HOLMES

ANTIDEPRESSANT-LIKE EFFECTS OF DAT OR NET, BUT NOT SERT, GENE KNOCKOUT IN THE FORCED SWIM TEST

FS HALL[1], MT PERONA[1], S WATERS[1], I SORA[2], KP LESCH[3], DL MURPHY[4], M CARON[5], GR UHL[1]

Antidepressant drugs produce therapeutic actions and many of their side effects *via* blockade of the plasma membrane transporters for serotonin (SERT), norepinephrine (NET) and dopamine (DAT). Many antidepressants block several of these transporters; some are more selective. Mice with knockouts of the genes that encode these transporters provide interesting models for effects of chronic antidepressant treatments. To examine the role of these monoamine transporters in depressive behavior forced swim test behavior was examined in DAT, NET and SERT knockout (KO) mice and wildtype littermates. DAT KO had the greatest antidepressant-like effects on forced swim test behavior, virtually eliminating immobility. In confirmation of previous findings, NET KO mice exhibited reduced immobility but SERT KO mice did not. Effects of DAT deletion were not simply due to hyperactivity. Decreased immobility was observed in DAT +/- mice that display modest alterations in locomotion as well as DAT -/- mice that display marked changes in locomotion. Struggling was increased, while swimming was almost eliminated in DAT -/- mice. Reduced struggling in combination with increased immobility has been observed in the FST in animal models of depression. Reduced expression of DAT thus produces effects complementary to models of depression that are larger than those produced by reduced expression of NET or SERT. These data support re-evaluation of the role of differences in DAT expression in the etiology of depression and the efficacy of direct blockade of DAT in treatment of depression. In particular these data raise the possibility that DAT gene variants, or reduced DAT expression, may complement other gene variants that increase predisposition to depression.

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THE ROLE OF MONOAMINERGIC GENE VARIATION IN DEPRESSIVE SYMPTOMOLOGY: LESSONS FROM A NON-HUMAN PRIMATE MODEL?

TK NEWMAN[1,2], CS BARR[1,2], JD HIGLEY[2], D GOLDMAN[1]

Candidate genes associated with behavioral and psychiatric disorders in humans have homologues in the rhesus macaque genome, an important animal model in behavioral and psychopharmacological genetics research. Some genes, including MAOA, 5-HTT and DRD4, contain functional polymorphisms that originated prior to the common ancestor of humans and rhesus, and show evidence of having been under positive selection. Depressive symptomology and mood disorder-like traits do not occur naturally in non-human primates, but can be elicited through acute and chronic stressful experiences. Previously characterized, as well as novel polymorphisms in rhesus macaque MAOA, 5-HTT, DRD4 and TPH2 genes show a complex pattern of influence on impulsivity, aggression, locomotory and self-directed behaviors that is mediated by non-genetic factors (e.g., peer-rearing). Though tentative at present, our results demonstrate the potential translational capacity of the rhesus model in investigating the role of "ancient" and novel monoaminergic gene polymorphisms on depressive-like behaviors, while emphasizing the value of cross-species comparative analysis of functional gene regions. The use of primate models may provide unique insights into the genetic etiology of affective illness.

1) Laboratory of Neurogenetics & 2) Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, NIH, USA.

NOREPINEPHRINE DEFICIENT MICE LACK RESPONSES TO ANTIDEPRESSANT DRUGS, INCLUDING SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

SA THOMAS[1], JF CRYAN[2], OF O'LEARY[2], S-H JIN[1], JC FRIEDLAND[1], M OUYANG[1], BR HIRSCH[1], A DALVI[2], I LUCKI[1,2]

Norepinephrine (NE) is thought to play an important role in the pathophysiology of depression and the mechanism of antidepressant action. Previously, mice were generated that are unable to synthesize NE and epinephrine due to targeted disruption of the dopamine □-hydroxylase gene (*Dbh*). To test the role of NE in mediating behavioral changes elicited by antidepressants, these mice were examined in the forced swim and tail suspension tests, in which antidepressants typically reduce immobility. There was no difference in baseline immobility between *Dbh*$^{-/-}$ mice and *Dbh*$^{+/-}$ controls that have normal levels of NE. In contrast to controls, antidepressant-like behavioral effects were either absent or greatly reduced in *Dbh*$^{-/-}$ mice following the administration of several classes of antidepressants. These included the NE reuptake inhibitors desipramine and reboxetine, the monoamine oxidase inhibitor pargyline, the atypical antidepressant bupropion, and the SSRIs fluoxetine, paroxetine and sertraline. One the other hand, the SSRI citalopram was equally effective in control and *Dbh*$^{-/-}$ mice. The restoration of NE reinstated antidepressant-like effects of both desipramine and paroxetine in the *Dbh*$^{-/-}$ mice. Consistent with the behavioral effects, citalopram but not fluoxetine elevated extracellular serotonin as assessed by microdialysis in the ventral hippocampus. The data show NE plays an important role in the acute actions of many antidepressants, including most SSRIs.

[1]Department of Pharmacology and [2]Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania USA. This research was supported by USPHS grants MH36262 and MH48125 (I.L.) and MH63352 (S.A.T.) from the National Institute of Mental Health and a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (S.A.T.).

ALLELIC VARIATION OF TRYPTOPHAN HYDROXYLASE-2 (*TPH2*) AND COMPLEX TRAITS: FROM DIFFERENTIAL BRAIN EXPRESSION TO FUNCTIONAL IMAGING

Klaus-Peter Lesch

Affective spectrum disorders is an etiologically heterogeneous group of brain disorders with complex genetics. Although research on their neurobiology is still in its infancy, several milestones have already been reached: Variation in gene expression were confirmed to play a predominant role in individual differences in complex traits including personality and behavior; gene x environment interaction were established in humans; gene-phenotype correlations were substantiated by functional neuroimaging; as well as the notion that both genes and environmental factors impact on brain development and thus set the stage for the susceptibility to affective spectrum disorders is increasingly appreciated. Variation in the tryptophan hydroxylase-2 gene (*TPH2*) coding for the rate-limiting enzyme of serotonin synthesis in the brain modulates responses of sensory and limbic circuits to emotional stimuli using event-related potentials and fMRI. *TPH2* variation has also been linked to a spectrum of clinical populations characterized by emotional dysregulation, including depression, bipolar disorder, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder but not panic disorder. Studies in murine and human brain confirmed that expression of TPH2 is specific to serotonergic neurons of the raphe, whereas the isoform TPH1 is expressed in the pineal gland but not other regions of the brain. Four common single nucleotide polymorphisms (SNPs) in and downstream of the transcriptional control region of *TPH2* have been tested for association with personality traits and disease risk in two cohorts comprising of 336 healthy individuals and 428 patients with personality disorders. Personality dimensions were assessed by the Tridimensional Personality Questionnaire (TPQ) and the revised NEO Personality Inventory (NEO-PI-R). Personality disorders were diagnosed with the Structured Clinical Interview of DSM-IV and were allocated to cluster A, B, and C. Individual SNP and haplotype analyses revealed significant differences in genotype frequencies between controls and cluster B as well as cluster C patients, respectively. In both patient groups, overrepresentation of T allele carriers of a functional polymorphism in the upstream regulatory region of *TPH2* (SNP G-703T, rs4570625) which biases the responsiveness of the amygdala, a structure critically involved in the modulation emotional behaviors, was observed. Furthermore,

significant effects of *TPH2* variants on anxiety-related traits defined primarily by the TPQ Harm Avoidance were found in healthy individuals. The results link functional *TPH2* variants to personality traits related to emotional instability as well as to cluster B and C personality disorders. These findings implicate alterations of 5-HT synthesis in emotion regulation and confirm *TPH2* as a susceptibility and/or modifier gene of affective spectrum disorders.Molecular and Clinical Psychobiology, Department of Psychiatry and Psychotherapy, University of Würzburg, Würzburg GERMANY.

OUTSTANDING YOUNG INVESTIGATOR ABSTRACTS

OUTSTANDING YOUNG INVESTIGATOR AWARDEE – GRADUATE STUDENT
DECREASED GLYCINE AFFINITY AT THE NMDA RECEPTOR RESULTS IN IMPAIRED SWITCHING BEHAVIORS IN MICE THAT ARE REVERSED BY D-SERINE

V LABRIE[1,2], T LIPINA[1], J RODER[1,2]

Several studies have implicated dysfunctional glutamatergic neurotransmission in the pathophysiology of schizophrenia. Pharmacological inhibition of the NMDA receptor produces behavioral deficits endotypic of schizophrenia, including impoverished switching capabilities. Latent inhibition and the Morris water maze were used to measure preservative behaviors in Grin1^{D481N} mice, which have an NMDA receptor with a reduced affinity for glycine. Latent inhibition (LI) examined the switching response of mice following 40 tone pre-expositions and 2 or 4 tone-shock associations. Grin1^{D481N} mice showed abnormally persistent LI, which was reversed by drugs that modulate the NMDA receptor glycine site, D-serine and ALX-5407, as well as by the traditional atypical antipsychotic, clozapine. Likewise, the NMDA receptor glycine site antagonist, L-701,324, produced persistent LI. In the water maze tasks, the platform was moved after either an extensive training period or daily to assess the delay in learning a new platform location. Grin1^{D481N} animals displayed a prolonged search for the previously acquired platform location, which was normalized by D-serine or additional training. Reduced glycine binding appears to model impairments in attentional set-shifting associated with negative symptoms of schizophrenia. These psychiatric symptoms may be ameliorated by antipsychotics that activate the NMDA receptor glycine site.

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OUTSTANDING YOUNG INVESTIGATOR AWARDEE – GRADUATE STUDENT
SHORT-TERM SELECTED LINES FOR FEAR CONDITIONING: QTL AND GENE EXPRESSION ANALYSIS

CA PONDER[1], TC GILLIAM[2], AA PALMER[2]

We used divergent selection for fear conditioning (FC), as measured by freezing in a context previously paired with a foot-shock, to investigate the genetic basis of FC. Starting with a C57BL/6J x DBA/2J F_2 population, we applied selection pressure for 4 generations to produce lines with extremely divergent FC. Using interval mapping we identified significant QTL on chromosomes 1, 13, 14, and 19 and suggestive QTL on chromosomes 4, 5, 10, and 11, with significance levels determined by permutation of the phenotype among individuals. We also compared the individual marker frequency in these QTL regions in each generation to test for differences between the lines resulting from selection, based on a method described by Belknap et al. (1997), and found significant differences in markers on chromosomes 1 and 19. We will also present a novel permutation approach to QTL analysis in selected lines that permutes the genotypes, therefore preserving the pedigree structure of the population. Finally, we examined gene expression differences in the amygdala and hippocampus of naïve male mice from the final selection generation. Using a Bayesian statistical analysis, we identified significant expression differences between the selected lines for about 100 transcripts. Data from www.genenetwork.org shows many of the identified transcripts have cis-expression QTL (eQTL). We then used quantitative PCR (qPCR) to follow

up on 19 of the represented genes, and qPCR results confirm many of the expression differences. We hypothesize that underlying eQTL are the cause of some of our behavioral QTL.
[1] Department of Genetics and Development, Columbia University, New York, New York USA and [2] Department of Human Genetics, University of Chicago, Chicago, Illinois USA. Supported by NIH grant MH70933, and an NARSAD Young Investigator Award.

OUTSTANDING YOUNG INVESTIGATOR AWARDEE – POSTDOCTORAL FELLOW
LOCALIZED EXPRESSION OF BETA2-CONTAINING NICOTINIC ACETYLCHOLINE RECEPTORS IN DOPAMINERGIC NEURONS IN MICE SUPPORTS LOCOMOTOR ACTIVATING, BUT NOT REWARDING EFFECTS OF NICOTINE
YS MINEUR[1], S KING[1,2], S GRADY[3], M MARKS[3], MR PICCIOTTO[1]

Viral mediated gene transfer has shown that nicotinic acetylcholine receptors (nAChRs) in the ventral tegmetal area (VTA) are essential for behaviors related to nicotine addiction (Maskos et al., Nature. 2005 Jul 7;436(7047):103-7), but cannot distinguish between nAChRs on dopaminergic or GABA neurons in the VTA. Further, existing pharmacological techniques cannot differentiate between the role of presynaptic nAChRs that augment neurotransmitter release and postsynaptic nAChRs that drive dopaminergic neuron firing directly. Moreover, although the role of the dopamine system in the psychomotor stimulant effects of nicotine is fairly well-established, it is not known whether nAChRs, on glutamate and GABA terminals impinging on the dopaminergic neurons are critical for nicotine reinforcement or whether nAChRs on dopaminergic neurons themselves are critical. Using mice with localized, conditional expression of the beta2 subunit of the nAChRs in dopaminergic neurons of the VTA, we demonstrate that beta2-containining nAChRs on dopaminergic neurons in the VTA 1) can support nicotine-elicited dopamine release from dopaminergic terminals in the nucleus accumbens, 2) can induce locomotor sensitization, but 3) cannot condition place preference for nicotine. These results reveal that nAChRs on dopaminergic neurons are sufficient for nicotine-mediated dopaminergic release and its psychostimulant action, but are not sufficient for nicotine reward.
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OUTSTANDING YOUNG INVESTIGATOR AWARDEE – JUNIOR FACULTY
THE HUMAN $GABA_A$ RECEPTOR $\alpha 2$ GENE (*GABRA2)*: FINDINGS FROM AN ALCOHOL ENDOPHENOTYPE STUDY AND POST-MORTEM BRAIN EXPRESSION ANAYLSES
HM HAUGHEY, P FINAN, R VILLANUEVA, G CHARNOSKI, KE HUTCHISON

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter within the CNS and is thought to play a role in several of the behavioral effectts of alcohol, including motor coordination, sedation, anxiolysis, tolerance, dependence, ethanol preference and symptoms of withdrawal (Buck, 1996; Grobin et al., 1998; Korpi et al., 1998). Recently studies by Edenberg et al. (2004) and Covault and colleagues (2004) have demonstrated an association between *GABRA2* and alcoholism. The present study had two aims: 1) to elucidate the extent to which SNPs within the *GABRA2* gene influence the acute subjective effects of alcohol; and 2) to determine the functional relevance of these SNPs by assessing post-mortem brain *GABRA2* mRNA levels. Our first aim was examined by taking an intermediate-based phenotype approach in which we assessed the acute subjective effects of alcohol in non-treatment seeking heavy alcohol drinkers. Results indicate that *GABRA2* SNP rs279858 and SNP rs573400 are in complete LD thus we will present data for SNP rs279858. The *GABRA2* SNP rs279858 demonstrated a significant interaction for alcohol x *GABRA2* x trial on the mood effects of happiness ($p<0.05$) and vigor ($p<0.02$), as measured by the Profile of Mood States (POMS) (McNair et al., 1971). SNP rs279858 was also found to have a significant main effect on ($p<0.04$) on the hedonic value of the alcohol. Our second aim used real-time PCR to quantitate human post-mortem Prefrontal Cortex *GABRA2* mRNA levels within 40 individuals, a main effect of SNP rs279858 on *GABRA2* mRNA level ($p<0.004$) was observed. In summary, the results of this study support previous findings that the GABAergic system plays a role in

brain mechanisms of reward and suggests that polymorphisms within the *GABRA2* gene may be useful at predicting future risk for alcoholism.
University of Colorado at Boulder, Department of Psychology, Boulder, Colorado USA.
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DISTINGUISHED SCIENTIST AWARD PLENARY LECTURE

GENETIC HERITABILITY: AN OLD BOTTLE FOR SOME 21ST CENTURY WINE
DOUGLAS WAHLSTEN

The term "heritability" is used in two ways in neurobehavioral genetics, (a) as a generic indicator of parent-offspring similarity or transmissibility, and (b) as ratio of genetic to phenotypic variance based on a purported partition of genetic (G) and environmental (E) causes of individual differences. Partitioning variance is valid only when the factors are additive (G + E), but we know from many studies of development and the environmental control of gene expression that additivity is biologically bogus. In research with animals, inbred strain comparisons or selective breeding are often used to assess heritability. These methods are sensitive to the maternal environment, indirect genetic effects, mitochondrial genes and other non-mendelian influences, including in some cases "cultural inheritance." Along with chromosomal genes, these multifarious causes of parent-offspring resemblance comprise the individual's more broadly construed heredity (H). Either the field must give up the use of "heritability" as a genetic parameter because there is no generally valid way to separate the influences of G versus E, or it must change the definition of heredity to be a more inclusive H rather than strictly mendelian G and regard "heritability" as a generic statistical indicator.Great Lakes Institute for Environmental Research, Department of Biological Sciences, University of Windsor, Ontario CANADA.

SYMPOSIUM V: "GENETIC AND EPIGENETIC DETERMINANTS OF SOCIAL BEHAVIOUR IN LABORATORY MODEL ORGANISMS," CHAIRED BY ENRICO ALLEVA AND ROBERT GERLAI

EFFECTS OF EARLY SOCIAL ENRICHMENT ON ADULT MOUSE SOCIAL PHENOTYPE
L RICCERI, I BRANCHI, E ALLEVA

In rodents, manipulations of the mother-infant interaction have consequences persisting for the entire life-span. To study the effects of early social experiences on brain development, we exploited a novel manipulation providing the mouse pup with an highly social stimulating environment: the communal nesting (CN). It consists in a single nest where three mothers keep their pups together and share care-giving behaviour from birth to weaning, mimicking the natural ecological niche of the mouse species. Compared to mice reared in standard nesting laboratory condition, CN pups were provided with higher levels of maternal care. At adulthood, CN mice displayed higher propensity to interact socially and achieved more promptly the behavioral profile of either dominant or subordinate male. Furthermore, CN adult mice showed higher NGF levels, which were further affected by social status, and higher BDNF levels in the brain. These findings are consistent with the hypothesis that alterations in the early social environment, which involve changes in parental care, affect brain and behavior development. They also indicate CN as a useful experimental strategy for the study of interactions between genetic and epigenetic determinants in shaping adult mouse social phenotype.
Section of of Behavioural Neuroscience, Dept Cell Biology and Neurosciences, Istituto Superiore di Sanità, Rome, ITALY. This research was supported by project ISS-NIH 0F14.

SOCIAL PLAY IN C57BL/6J AND BTBR T+ tf/J MICE
HG MCFARLANE[1, 2], JN CRAWLEY[1]

Abnormal communications and social interactions are among the main features of autism spectrum disorders (ASDs) and finding or developing a genetic strain of mice that model these features would be beneficial to ASD research. Previous research (Moy et al, submitted) suggests that the BTBR T+ tf/J mice

show less social approach in our three-chambered social task. Therefore, the aim of the present study was to perform a detailed assessment of the juvenile play and social behaviors of BTBR T^+ tf/J and C57BL/6J mice. 21 day old male mice were separated and housed individually for approximately 2 hours. Following this isolation period, pairs of same strain subjects of similar body weight but from different litters were placed in the Noldus PhenoTyper and their behavior recorded for 30 minutes. All experiments were carried out during the first half of the dark phase of the light cycle in a dimly lit room illuminated by a single red lamp. Frame by frame behavioral analyses of the play pairs were later carried out using the Noldus Observer 5.0 software. On several measures of social interaction and play, juvenile BTBR T^+ tf/J mice were found to engage in significantly fewer bouts than did their C57BL/6J counterparts. BTBR T^+ tf/J mice were also found to engage in significantly longer bouts of self grooming behaviors and to be less active in the play arena than C57BL/6J mice. However, in an open field test, BTBR T^+ tf/J mice were more active than C57BL/6J mice, suggesting that their diminished activity in the play arena was not due to an overall diminished locomotor ability. Further, in the three chambered social approach task, BTBR T^+ tf/J mice also showed significantly lower social approach than their C57BL/6J counterparts, replicating Moy et al (submitted). These results suggest that BTBR T^+ tf/J mice may serve as a model of diminished sociability for ASD research.

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THE ROLE OF THE MATERNAL ENVIRONMENT IN THE DEVELOPMENT OF ALTERNATIVE BEHAVIOURAL PHENOTYPES IN MICE

JP CURLEY[1], FA CHAMPAGNE[1,2], EB KEVERNE[1], PPG BATESON[1]

Variation in maternal behaviour (licking/grooming, nursing, nestbuilding, retrieving) in mice may be mediated via both genetic and environmental factors. Using inbred, hybrid and outbred mouse strains, as well as gene knockout mice, we have established a genetic basis for the regulation of maternal care, with differences in the patterns of these behaviours being related to the relative density of oxytocin receptors. We also show that the levels of postpartum care invested in offspring by a mother can be regulated by other factors such as her early life and adult experiences. From an evolutionary perspective, variation in maternal behaviour has important consequences for the adult behaviour of offspring, providing information about the likely external environment and how best to develop. We demonstrate that variation in the quality of early life experiences leads to changes in the adult levels of exploration, activity and anxiety of offspring, and that this may be transmitted in a non-genomic fashion to future generations. We also show that the most likely mechanism for this trans-generational inheritance is a behavioural transmission of maternal care from mother to daughter.

[1]Sub-Department of Animal Behaviour, University of Cambridge, Cambridge, UK and [2]Department of Psychology, Columbia University, New York USA. This work was supported by grants form the Leverhulme Trust, BBSRC & Canadian Institutes of Health Research.

SOCIAL BEHAVIOUR OF ZEBRAFISH: A TARGET OF MUTAGENESIS?

R GERLAI, C BUSKE, N MILLER

Zebrafish has been a favourite of genetics and developmental biology due to its prolific nature, small size, and transparent externally developing embryo. Recently, however, increasing number of studies has been devoted to the behavioural analysis of this species. Some of these studies show that behavioural phenotypes may be used as screening criteria in forward genetic, i.e. mutagenesis studies. Particularly interesting is the social behaviour of zebrafish. Zebrafish forms groups within which individuals swim in close proximity to each other. The adaptive significance of this behaviour is thought to be predator avoidance as the attention of fish predators may be divided among the multiple moving targets. However, it appears that zebrafish shows strong preference for its own kind and do not mix with other species. Thus the shoaling behaviour may have other functional explanation as well. This paper will review what is known about zebrafish social behaviours and will also present some preliminary observations on the effects of some factors, including a predator model, dispersed food, and drug

(alcohol) exposure on group cohesion. Furthermore, we will present a new method, a simple computer software, with which we quantify shoaling behaviour. The paper will discuss questions with regard to the construct validity of zebarfish social behaviour for human brain function, i.e. whether the mechanisms underlying zebrafish and human social behaviours could be similar and whether zebrafish may be used to screen for genetic factors underlying human brain disorders associated with abnormalities of social behaviours, including autism spectrum disorders.
University of Toronto at Missisauga, Mississauga, Ontario CANADA.

POSTER SESSION ABSTRACTS (Alphabetical by first author)

INTELLIGENTFLY DESIGN: EXPERIMENTAL EVOLUTION AS A STRATEGY TO IDENTIFY GENETIC INTERACTIONS AMONG MEMORY MUTANTS

A ALTICK, E KOCKENMEISTER, P MITRA, J DUBNAU

Genetic screens in flies have identified a large number of genes involved in learning and memory. In few cases, however, have mechanistic connections been made between individual genes. This is due largely to the practical impossibility of conducting second site modifier screens with this complex phenotype. The most notable exception is the cAMP pathway. Two components of this signaling system (dunce and rutabaga) were identified by forward mutagenesis, and reverse genetic approaches have established roles in memory for multiple additional elements of this pathway. However, there clearly are cAMP independent forms of learning because even null alleles of rutabaga adenlylyl cyclase (or of dunce, or PKA catalytic or regulatory subunits) have residual memory in a Pavlovian olfactory task. We recently have identified 57 transposon-tagged alleles, which confer memory defects when assayed in an olfactory conditioning paradigm (Dubnau 2003). We are now using artificial selection to identify combinations of these alleles that are capable of suppressing the rutabaga mutant phenotype. We have created a founding population of flies that are homozygous for the rutabaga1 mutation and are heterogeneous with respect to transposon insertions at each of the additional 57 loci. We are using selective breeding over multiple generations to “evolve” allelic combinations capable of suppressing the rutabaga mutant phenotype. With PCR, we are able to track the occurrence of each of the 57 alleles within the populations and within individual flies. We expect to find correlations between co-occurrence of subsets the 57 alleles and rutabaga suppression, thus elucidating more complex networks of genes which function in parallel to the cAMP pathway in learning.
Cold Spring Harbor Laboratory, Cold Spring Harbor, New York USA. Funding Support provided by Beckman Young Investigator Award and DART Neuroscience Alliance.

ALTERED DOPAMINERGIC NEURONAL DEVELOPMENT IN D2R MICE: POSSIBLE ROLE OF D2R-MEDIATED SIGNALING IN NEURAL PLASTICITY

SUNG Y KIM, MS CHANG, SA Y KIM, Y-S NA, JE LEE, BK JIN, BH LEE, J-H BAIK

As the dopaminergic pathways in the midbrain have been closely associated with serious neuro-psychiatric disorders, the elucidation of the mechanisms underlying dopaminergic neuronal development should provide some important clues for related disorders. In mice lacking the dopamine D2 receptor (D2R-/-), stereological cell counting analysis showed that the number of mesencephalic tyrosine hydroxylase cells was significantly low during ontogeny, as compared to that observed in wild-type (WT) mice, thereby indicating an alteration in dopaminergic neuronal development in the absence of D2R. The results of immunohistochemical and RT-PCR analyses revealed that the expression of Nurr1, an orphan nuclear receptor, as well as Ptx3 expression, was selectively reduced in D2R-/- mice during the embryonic stage. A reporter gene assay using the Nur response element linked to the luciferase reporter gene indicated that the stimulation of D2R results in the activation of the Nurr1-mediated reporter gene. This D2R-mediated NurRE-dependent transcriptional activity was regulated via the activation of extracellular-signal regulated kinase (ERK). Furthermore, quinpirole treatment was shown to elicit an increase in the number of TH-positive neurons, as well as the neuritic extension of TH neurons, coupled with ERK activation and Nurr1 activation in the TH positive neurons in primary mesencephalic cultures

from WT mice. However, this regulation was not detected in the D2R-/- mice. These results suggest that signaling through D2R in association with Nurr1 employing ERK, plays a critical role in mesencephalic dopaminergic neuronal development.
Korea University, Seoul, KOREA. This work was supported by a research grant from the Molecular and Cellular Biodiscovery Program (grant No. M1-0311-00-0069), by basic research grant from KOSEF (Grant No. R01-2004-000-10671-0) and by a grant (Grant No. M103KV010020-03K2201-02030, M103KV010020-05K2201-02030) from the Brain Research.

CONFIRMATION AND FINE MAPPING OF ETHANOL SENSITIVITY QTLs, AND CANDIDATE GENE TESTING IN THE LXS RECOMBINANT INBRED MICE
B BENNETT, P CAROSONE-LINK, TE JOHNSON
In previous studies we have mapped quantitative trait loci (QTLs) for hypnotic sensitivity to ethanol using a small recombinant inbred (RI) panel and a large F2 backcross. This behavior is the most significant predictor of long term risk for alcoholism. We remapped hypnotic sensitivity using a new set of 75 RI strains, the LXS, derived from inbred Long Sleep (ILS) and inbred Short Sleep (ISS) strains. We expected to improve mapping resolution in the QTL regions and to identify novel QTLs for loss of the righting reflex following ethanol (LORE). Large RI panels are advantageous for genetic mapping for a number of reasons, including enhanced precision of map location, and extensive resampling of identical genotypes. We used three common mapping algorithms (R/qtl, QTL Cartographer, and WebQTL) to map QTLs in the LXS, and compared the results. Most mapping studies use only a single algorithm, an approach which may result in failure to identify minor QTLs. We confirmed most of our previously reported QTLs, although one major QTL from earlier work (Lore2) failed to replicate, possibly because it represented multiple linked genes separated by recombination in the RI strains. We also report narrowed confidence intervals, based on mapping with a new genetic resource of over 4000 polymorphic SNP markers. These narrowed confidence intervals will facilitate candidate gene identification, and assessment of overlap with human regions specifying risk for alcoholism. Finally, we present an approach for utilizing these RI strains to assess evidence for candidate genes in the narrowed intervals, and apply this method to a strong candidate, the serotonin transporter.
University of Colorado, Boulder Colorado USA. This work was supported by grants from the NIH (RO1 AA11984 (TEJ), (AA014666 and DA015663) the Ellison Foundation for Medical Research (TEJ), and by funds from the University of Colorado.

GENETIC BASIS OF LICK RATE AND LICK MICROSTRUCTURE IN MICE
JD BOUGHTER Jr, JP BAIRD, SJ ST. JOHN, RW WILLIAMS, L LU, D HECK
Fluid licking in mice is thought to be under the control of one or more central pattern generators (CPGs). We compared 20-min water intake of two water restricted inbred strains of mice, C57BL/6J (B6) and DBA/2J (D2), using a contact lickometer. Results indicate that D2 mice lick at a faster rate: Using a 1 sec burst-pause criterion, D2 mice licked 7% faster on average within bursts (7.09 vs. 6.62 lick/s). These differences in lick rate were not due to a difference in tongue length or weight. Interestingly, the mode of the interlick interval (ILI) distribution for D2 mice indicated a 19% faster rate of licking than B6 mice (10.06 vs. 8.43 licks/s). This disparity was due to the presence of proportionally more ILIs that were roughly twice (180-200ms) the peak of the ILI mode in D2 mice vs. B6 mice. These ILIs are thought to represent missed licks or taste reactivity movements (e.g., lateral tongue protrusions). A strain difference also existed with respect to bursts and pauses. For both groups the average burst size was almost identical (36 licks/burst) but the mean burst duration was shorter for D2 vs. B6 mice, consistent with the faster lick rate of D2 mice. Strikingly, D2 mice expressed an average pause length almost 55 seconds longer than that for B6 mice (140s vs. 85s), resulting in an overall slower rate of ingestion for D2 mice over the course the drinking period. In order to estimate the role of genetic factors on lick rate, we produced generations of F1 and F2 mice, and tested a set (n = 26 strains) of BXD RI mice. Using these mapping populations, we estimated heritability of lick rate > 0.50, with no fewer than 3 polymorphic genes contributing to the genetic variance. Preliminary QTL analysis indicates loci on Chr 1, 2, 5 and 10 contributing to variation in lick rate. Overall, results suggest a fundamental difference in the rhythmic rate

of licking and the organization of pauses between bursts in B6 and D2 mice, likely due to strain variations both within the CPG itself and in processes that engage and disengage the CPG.
University of Tennessee Health Science Center, Memphis, Tennessee USA.

BEHAVIORAL RESPONSES OF 129/SV, C57BL/6J AND DBA/2J MICE TO A NON-PREDATOR AVERSIVE OLFACTORY STIMULUS
F CAPONE, A VENEROSI, I BRANCHI, F CIRULLI, E ALLEVA
Adult males of three inbred mouse strains (129/SvPasIco, C57BL/6J, and DBA/2J) were exposed to a worm-shaped sponge soaked with the chemical component of the aversive scent (toluquinone odor) naturally secreted by a myriapod species (Ommatoiulus sabulosus) in the presence of a vertebrate predator. Subjects were exposed to the sponge for three consecutive days. Behavioral responses to the toluquinone odor were characterized both by an approach phase of risk assessment and by a repeated series of approach-avoidance episodes. Toluquinone exposure reduced completely, and in a strain-independent fashion, selected behaviors such as crouching, catching and chewing the sponge. Other responses were strain-dependent: the DBA strain displayed defensive burying at high levels, C57 mice performed high levels of withdrawal while the 129/Sv strain showed also high levels of stretch attend posture. Compared to other tasks, this test is an ethological (i.e. molded by strong evolutionary force), simple, cheap and is not affected by strain differences in appetitive-sensory responses, as shown by the strain-independent responses. These features make this task as a good complement to any exploration-anxiety test battery, also assessing for potential olfactory deficits of mutant strains.Section of Behavioral Neurosciences, Dept of Cell Biology and Neurosciences, Istituto Superiore di Sanita, Viale Regina Elena 299, Roma ITALY. This study was supported by project NIH-ISS Rif. 0F14.

GENE-TO-PHENOTYPE NETWORKS FOR BRAIN AND BEHAVIOR
EJ CHESLER, R KIROVA, A PERKINS, MA LANGSTON
Heritable polymorphisms cause minute structural and functional changes in DNA that exert their effects in a cascade of activity traversing many levels of biological scale from molecular to gross structure, function and behavior. New techniques for high-througput molecular analysis and the availability of larger and increasingly well-characterized reference populations has rendered feasible the large scale extraction of these networks of activity. Using both combinatorial and parametric approaches, network graphs can be constructed and decomposed to discover and characterize polygenic and pleiotropic networks of central nervous system structure and function. These graphs include genotypes, QTL models, molecular endophenotypes, brain morphology and behavior. The decomposition of high throughput molecular data prior to mapping facilitates the discovery of the role of multi-locus interactions in these networks. These genome-phenome integration techniques suggest an approach for empirical discovery of the ontology of complex behavior.Oak Ridge National Laboratory, Oak Ridge, Tennessee USA. Funding support provided by NIAAA Integrative Neuroscience Initiative on Alcoholism Pilot Grant to EJC.

EFFECTS OF ALCOHOL ON FEAR-POTENTIATED STARTLE IN MICE SELECTIVELY BRED FOR HIGH (HAP) OR LOW (LAP) ALCOHOL PREFERENCE
JA CHESTER
The purpose of this study was to investigate the genetic propensity to develop learned fear and the effects of alcohol on the expression of learned fear in mice selectively bred for high or low alcohol preference. Alcohol-naïve, male and female high- (HAP1) and low- (LAP1) alcohol-preferring mice were randomly assigned to a FEAR-CONDITIONED or CONTROL group. Mice in the FEAR-CONDITIONED group received 20 pairings of light + footshock (light: 7W, 30s; shock: 0.8 mA, 0.5s; 2 min ITI). Within each conditioning group, mice received either saline or one of three alcohol doses (0.5, 0.75, 1.0 g/kg IP) 30 min prior to the FPS testing session. Both male and female HAP1 mice showed greater FPS magnitude than male and female LAP1 mice. CONTROL groups showed no FPS. Alcohol at the doses tested did not influence the expression of FPS in either the HAP1 or the LAP1 lines. These results indicate that mice selectively bred for high-alcohol-preference are more susceptible toward the development of anxiety-related behavior than their low-alcohol-preferring counterparts, as measured

using the FPS paradigm. We are currently testing whether similar effects are seen in the replicate 2 HAP/LAP mouse lines.Psychological Sciences, Purdue University, West Lafayette, Indiana USA.

A NEW MOUSE MODEL OF HIGH ALCOHOL SELF-ADMINISTRATION: SELECTION FOR HIGH DRINKING IN THE DARK

J CRABBE[1], J RHODES[2]

Many animal models have targeted alcohol abuse and dependence. In the rodent, the majority of such models have sought to increase alcohol self-administration using genetic or environmental manipulations, or their combination. Strictly genetic manipulations (e.g. comparison of inbred strains or targeted mutants, selective breeding) have not yielded rat or mouse genotypes that will voluntarily self-administer to the point of intoxication. While some behavioral manipulations (e.g., scheduling and or limiting access to alcohol) will induce mice or rats to self-administer alcohol to intoxication, these typically require significant food or water restriction and/or a long time to develop. Relatively high-intake genotypes do not appear to be preferentially susceptible to these effective behavioral manipulations. Some human alcoholics repeatedly drink to intoxication, even in the face of substantial physical and social feedback opposing this behavior. It would be useful to have a mouse genetic animal model that self-administers sufficient alcohol to become intoxicated. We review our progress toward that goal. In one set of experiments, we are selectively breeding High Drinking in the Dark mice to ingest 20% alcohol until they reach blood alcohol levels (BALs) exceeding 100 mg%. After three generations of selection, more than 25% of the population exceeds these BALs. These mice should be useful for mechanistic studies, and for pharmacological experiments designed to limit alcohol self-administration. [1]Portland Alcohol Research Center, Department of Behavioral Neuroscience, Oregon Health & Science University, and VA Medical Center, Portland Oregon 97239 USA. [2]Beckman Institute and Department of Psychology, University of Illinois at Urbana-Champaign, Urbana Illinois 61801 USA. Supported by the NIH-NIAAA Integrative Neuroscience Initiative on Alcoholism (AA13519), NIH-NIAAA Center Grant AA10760, and the US Department of Veterans Affairs.

WHEEL RUNNING AS A TOOL TO MEASURE BEHAVIOURAL SENSITIZATION

L DE VISSER, AK STOKER, BM SPRUIJT, R VAN DEN BOS

Wheel running is an extensively used indicator for locomotor activity in neurobiological research. However, recent studies suggest running wheel activity to be naturally Rewarding and reinforcing; it may be described as an incentive-motivated behaviour, similar to the intake of addictive drugs. We previously showed that providing mice with a running wheel has the potential to disrupt the daily organization of behaviour. In the present study, we investigated the influence of novelty-induced stress on wheel running in two inbred strains of mice (C57BL/6 and DBA/2). Our aim was to determine whether wheel running can be used as a tool to study both genetic and environmentally induced differences in sensitivity to rewarding behaviours in mice. One group of male mice (n=12 per strain) was placed in an automated home cage observation system (PhenoTyper®, Noldus Information Technology, Wageningen, The Netherlands) for two weeks with a wheel integrated in the cage. A second group of mice (n=12 per strain) was allowed to habituate to the novel cage for one week before a running wheel was introduced. Locomotor patterns and running wheel activity were recorded continuously. Results showed a pronounced sensitising effect of novelty on the intensity of wheel running in C57Bl/6 mice. In DBA/2 mice no such effect could be detected. Overall levels of wheel running were higher in DBA/2 mice under both novelty and habituated conditions. Furthermore, both strains showed a sensitised response when the wheel was returned after one week of removal. From these findings we put forward the suggestion that wheel running behaviour could serve as a tool to study the interaction between genetic and environmental factors in behavioural sensitisation in mice. As it is displayed spontaneously and easy to monitor, wheel running may be well suitable to be included in high-throughput phenotyping assays. This work was supported by ABC Neurogenomics and Utrecht University, Utrecht, THE NETHERLANDS.

SEX DIFFERENCES IN ETHANOL WITHDRAWAL BETWEEN MALE AND FEMALE RATS
LL DEVAUD, PE ALELE

Investigations of responses to chronic ethanol consumption and withdrawal have uncovered significant sex differences in the increased seizure risk of withdrawal. For example, female rats had seizure thresholds restored to basal levels by 3 days of withdrawal (EW) whereas male rats still showed a significantly increased seizure susceptibility. Surprisingly, acute administration of 2.5 g/kg ethanol had a greater anticonvulsant effect against bicuculline-induced seizures in early EW compared to pair-fed control responses, which was enhanced for female rats at 3 days EW. In contrast, ethanol had a significant anticonvulsant effect against pentylenetetrazol (PTZ) induced seizure risk in pair-fed control animals, with reduced effect in both male and females during EW. As these data suggest that a number of factors influence EW behaviors, with shifts from sensitization to tolerance during EW recovery, we next tested a bolus injection of PTZ to assess additional seizure signs. Ethanol (2.5 g/kg) increased seizure latency in all treatment groups at the 24 hr EW time. At 3 days EW, ethanol increased latency by 32% in males whereas EW females now showed a reduced response to ethanol, suggestive of tolerance. Additionally, ethanol-treated EW females showed a significantly greater reduction in seizure severity, from a maximal score of 8 (death) to a minimal score of 0 (brief signs). In contrast, severity scores in male were reduced, from 4.25 to 0. Ethanol reduced seizure duration more in EW females than male rats at 24 hours EW and reduced severity more in EW males (6 to 0) and OVX (6.3 to 0), than intact females (3.5 to 1.6) at 3 days EW. These data further support the suggestion that genetic differences as basic as those conferring one's sex, influence ethanol withdrawal-induced seizure risk differentially between male and female rats.Idaho State University, Pocatello, Idaho USA. This work was supported by NIH grants AA110877 (LLD) and P20RR01654 (PEA).

INTERLEUKIN-7 RECEPTOR KNOCKOUT MICE DISPLAY DEFICITS IN HABITUATION
AF DORMAN[1,2], VJ BOLIVAR[1,2], R PIETROPAOLO[1], B HERRON[1,2], L FLAHERTY[1,2]

Cytokines are primarily known for their roles in inflammation and immunity; however, recent studies indicate that some cytokines (e.g. IL-1α, IL-2, IL-6) influence behavior. We demonstrate that interleukin-7 receptor knockout (B6.129S7-Il7r^{tm1Imx}/J) mice exhibit behavioral deficits in open field activity and habituation relative to C57BL6/J (B6) mice. In contrast, IL7$^{-/-}$ mice do not exhibit habituation deficits, indicating that a novel ligand interacts with the IL-7 receptor to elicit the observed behavior. The hippocampus is involved in learning and memory processes, e.g. habituation. Previous studies have indicated that hippocampal mossy fiber length correlates with some learning and memory phenotypes; however, our analysis of IL7R$^{-/-}$ and B6 mossy fibers revealed no significant differences. We performed global gene expression analyses of IL7R$^{-/-}$ and B6 hippocampi to determine if they differed in gene expression. We identified 66 probe sets that are differentially expressed between the two strains ($p<0.05$) by the Benjamini-Hochberg FDR), including genes implicated in synaptic plasticity, long-term potentiation, and neuronal migration. Our results suggest a novel role for the IL-7 receptor in behavior.[1] Genomics Institute, Wadsworth Center, Troy, New York USA. [2] School of Public Health, Department of Biomedical Sciences, University at Albany, Albany, New York USA.

SPATIAL-COGNITION RELATED CHARACTERISTICS IN MOUSE OPEN-FIELD BEHAVIOR
A DVORKIN[1], Y BENJAMINI[2], I GOLANI[1]

In previous studies of Open-Field behavior in rodents, it was shown that rats establish preferred locations (home-bases) and principal places. The vast majority of exploratory behavior is organized around these locations, which are characterized by high number of visits and high cumulative time spent in them. In the present study, we examine the dynamics of visiting behavior to locations in the open-field in mice. A visit is defined as either passing through the location or stopping there. We estimate the probability of stopping at a location as a function of the number of previous visits to that location. This estimate can be regarded as a measure of the familiarity of the mouse with the location. A comparison of 3 inbred strains shows that, one strain (CZECHII/Ei) exhibits an overall increase in probability, another (DBA/2J), exhibits a fixed probability, and a third strain (C57BL/6J) shows a mild increase in this probability. The strain difference is not due to change in the rate of stopping, which remains constant in time in all 3 strains. An

increasing probability of stopping at a certain location is likely to reflect a memory of the history of visits to that location. This feature appears therefore to be a cognition-related measure of open-field behavior. The poor performance of DBA mice coincides with previous reports of impaired spatial memory due to hippocampal dysfunction in this strain.[1]Department of Zoology, George S. Wise Faculty of Life Sciences, and [2]Department of Statistics and Operations Research, The Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv, ISRAEL 69978. This research was supported by National Institute of Neurological Disorders and Stroke Grant R01-NS-40234-01. Generous funds from AstraZeneca were used to defray the cost of mice through the Mouse Phenome Project Collaborations Program.

A NOVEL GENETIC MODEL OF DEPRESSION
R GERSNER, D DAR, A ZANGEN

Depression is among the most prevalent forms of mental illness, but the neurobiological basis of depressive behavior is poorly understood. Many of the rodent models for depression are based on the assumption that depression is a response to acute or chronic stress. Other models are based on assumption of a certain biochemical dysfunction that underlies depression, while there is no consensus on the biochemical basis of depression. The diagnostic criteria for depression include several symptoms and it has also become clear that the risk for depression is partially genetic. We were therefore encouraged to investigate genetic factors of depressive behavior by establishing a novel animal model for depression based on selective breeding for a depressive phenotype. The selective breeding is based on tests that cover the core symptoms: loss of interest (using an exploration test in automatic locomotion boxes), lack of motivation (using a modified swimming test), anhedonia (using the sucrose preference test) and reduced energy/fatigue by chronically screening locomotor activity (using home-cage-based locomotion system). We found at the fourth generation of descendants a significant differences between "depressed", "normal" and "motivated" rats in the swimming test, in the sucrose preference test, in the basal locomotor activity at young ages and in some aspects of exploration. We expect this model to allow the study of the genetic contribution to depressive and motivated behaviors and the neurochemical characterization of these behaviors. In the near future we will test effectiveness of antidepressant drugs in this unique model.Department of Neurobiology, Feinberg Graduate School of the Weizmann Institute of Science, Rehovot, ISRAEL.

THE ROLE OF GENES IMPORTANT FOR DOPAMINE NEUROTRANSMISSION IN MECHANOSENSORY HABITUATION IN *Caenorhabditis elegans*
AC GILES[1,2], JH WEIRICH[2], WC HSU[2], HL LAU[2], CH RANKIN[1,2,3]

Caenorhabditis elegans is an excellent animal model for the analysis of the cellular and molecular mechanisms involved in learning and memory because it contains only 302 identified neurons and can be easily manipulated using genetic tools. These animals have been shown to possess both short- and long-term memory for habituation of the tap withdrawal response. Recent evidence suggests that a D1-like dopamine receptor homolog gene is expressed in the mechanosensory neurons of the tap withdrawal circuit. We hypothesized that dopamine might play an important role in modulating this circuit and therefore could play a role in habituation of the tap withdrawal response. Mutant strains of *C. elegans* with deficits in their dopaminergic neurotransmission, *cat-2* (tyrosine hydroxlase mutation) who lack the ability to synthesize normal amounts of dopamine, *dop-1* (dopamine receptor mutation) who lack the D1-like receptor homolog and *dat-1* (dopamine transporter mutation) who lack the dopamine reuptake transporter, were tested for both short- and long-term memory for habituation. All three mutants appeared to show approximately normal short-term habituation; however, none of the strains showed any evidence of long-term memory. This suggests that these gene are important in modulating the synaptic plasticity involved in long-term memory of this response. Interestingly, the hypothesized site of plasticity within the tap withdrawal circuit is a glutamatergic synapse, and dopamine has been found to modulate glutamatergic neurotransmission in other organisms. We are presently investigating whether the observed memory deficits in these mutants can be rescued: *cat-2* by the application of exogenous dopamine and *dop-1* by a wild-type *dop-1* transgene.[1]Graduate Program in Neuroscience, [2]Brain

Research Centre, [3]Psychology Department, University of British Columbia, Vancouver, British Columbia CANADA. Supported by NSERC to CHR.

ANALYSIS OF GENE EXPRESSION PROFILES OF *wdl* MOUSE – A MODEL OF CARBONIC ANHYDRASE-RELATED PROTEIN VIII DEFICIENCY

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The waddles (*wdl*) mouse is a unique animal model that exhibits ataxia and appendicular dystonia without pathological abnormalities of either the central or peripheral nervous systems. Previously, we detected a 19 bp deletion in exon 8 of the carbonic anhydrase-related protein VIII gene (*Car8*) within the *wdl* locus on mouse Chr 4 from *wdl* mice. Although we showed that CAR8 is virtually absent in *wdl* mice. The common Purkinje cell marker, calbindin, and the an intracellular IP3-gated Ca^{2+} channel, inositol 1,4,5-triphosphate receptor 1 (IP3R1), showed no difference between normal and mutant mice. In order to explore the potential pathways that Car8 causes the *wdl* phenotype, gene expression profiles of *wdl* mice was analyses using microarray technology. Our analysis showed that CAR8 deficiency has substantial effects on cerebellar gene expression profiles. A comparison between control and *wdl* mice identified 32 upregulated and 79 downregulated genes, which showed at least 2-fold changes, respectively, with an estimated false discovery rate of 5% or less. Several potentially important genes then were confirmed by semi quantitative PCR. According to the functions of differently expressed genes in *wdl* mice, a pathway involved in Car8 has been proposed. *Department of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee; †Departments of Orthopaedic Surgery-Campbell Clinic and Pathology, University of Tennessee Health Science Center, Memphis, Tennessee; ‡Departments of Neurology and Anatomy & Neurobiology, University of Tennessee Health Science Center, Memphis, Tennessee; §The Jackson Laboratory, Bar Harbor, Maine; ¶Functional Genomics Facility, University of Chicago, Chicago, Illinois; ‖Department of Chemistry and Biochemistry, University of Oklahoma, Norman, Oklahoma USA.Support for this work is from the UTHSC Center of Genomics and Bioinformatics (W.G.) and Center in Connective Tissue Research (W.G.). Additional support is from Dystonia Medical Research Foundation (M.S.L.); Veterans Administration (W.G); National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health (R01 AR51190 to W.G; R01 AR050785 to J.S.; RR01183 to L.R.D.); National Eye Institute, National Institutes of Health (R01 EY12232 to M.S.L.); National Institute of Neurological Diseases and Stroke, National Institutes of Health (R01 NS048458 to M.S.L.).

EFFECT OF COMBINED DOPAMINE RECEPTOR D2/SEROTONIN TRANSPORTER GENE KNOCKOUT ON THE BEHAVIORAL EFFECTS OF COCAINE

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Investigations into the mechanisms underlying the behavioral effects of cocaine have recently revealed the importance of uptake blockade of the neuronal plasma membrane transporter for serotonin (SERT), in addition to dopamine (DAT). For instance, although deletion of the DAT gene alone did not block cocaine reward, combined knockout of the DAT and SERT genes completely blocked cocaine conditioned place preference. Further implicating the combined importance of dopamine and serotonin systems in the behavioral effects of cocaine, studies have demonstrated that manipulations of several serotonin receptor subtypes modulate the rewarding and locomotor stimulant effects of cocaine; these include the serotonin 1A receptor, the serotonin 1B receptor, and the serotonin 2C receptor. Additionally, dopamine receptors including the D2 receptor subtype (DRD2) have been shown to affect cocaine reward as well. To further explore dopamine-serotonin interactions in cocaine reward and locomotion, the effects of combined gene deletions of SERT and DRD2 were examined. Consistent with the effects of each of these genes separately, combined SERT and DRD2 KO was found to increase cocaine conditioned preference alone or in combination, although the effect of SERT was much greater. These data contrast with the consequences of combined knockout on locomotor activity, under all conditions basal or drug-stimulated, which were largely affected by DRD2 KO, and only subtlety by SERT KO. The

importance of these findings is discussed in terms of the polygenic nature of drug abuse, and the potential contributions of human variants of these genes to abuse liability.
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BEHAVIOURAL PHENOTYPING METHODS IN THE GERMAN MOUSE CLINIC, AN OPEN ACCESS PHENOTYPING PLATFORM

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The German Mouse Clinic (GMC) (http://www.gsf.de/ieg/gmc) is an open access phenotyping platform, aiming at the establishment of mouse models of human diseases and the use of these models to study molecular disease mechanisms. To enhance reproducibility, standard operating procedures (SOPs) are developed in cooperation with European partners within the integrated EU-project EUMORPHIA (http://www.eumorphia.org). Within the GMC, behavioural phenotyping is focused on the detection of endophenotypes relevant for human brain dysfunctions, such as anxiety and mood disorders, schizophrenia, attentional and other cognitive deficits, and Parkinson's disease. To be comprehensive, but also efficient, the analysis is set up in a hierarchical way, starting with the primary screen. This analysis level consists of the modified Hole Board test, which was specifically developed for effective high-throughput behavioural analysis of lab rodents. The secondary screen level contains tests for locomotor, exploratory, emotional and social behaviour (e.g. dark-light transition, elevated plus-maze, open field, social interaction, olfactory perception). Furthermore, at this point functionality of sensorimotor competence and sensorimotor integration are assessed by acoustic startle reflex and pre-pulse inhibition. On the tertiary screen level various aspects of cognitive performance are being evaluated. Methods include procedures for the Five choice serial reaction time task (evaluating sustained and divided attention, attentional span and capacity, distractibility), fear-potentiated startle (fear memory, aversive), object recognition memory (appetitive) and social discrimination (social recognition memory, appetitive). Here we present (1) a short description of our primary screen procedure (modified Hole Board test) as well as an evaluation of its efficiency in detecting alterations in locomotion, exploration, anxiety-related behaviour, social affinity and object recognition memory; (2) an overview of our secondary and tertiary screen procedures and (3) short descriptions of our procedures used for pre-pulse inhibition, social interaction, social discrimination and object recognition, as well as example data of phenotypes detected by their use.Institutes of [1]Developmental Genetics and [2]Experimental Genetics, GSF – National Research Centre for Environment and Health, Neuherberg, GERMANY. Supported by European Commission under FP5 No. QLG2-CT-2002-00930 and NGFN (grant No. 01GR0430).

AMYLOID PATHOLOGY IS DISSOCIATED FORM MEMORY IMPAIRMENT IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Amyloid beta (Aβ) is the major component of senile plaques found in the brains of Alzheimer's disease (AD) patients, and notably the presence of numerous neuritic amyloid plaques is required for a diagnosis of AD. There is a supporting evidence that soluble species of Aβ play an important role in mediating initial pathological events in AD, and can provide a reliable predictor of developing dementia. To better understand the role of individual Aβ peptides in dementia we have evaluated the cognitive status of novel BRI-Aβ mice that over-express Aβ in the absence of amyloid β precursor protein (APP). BRI-Aβ40 express 2-3 fold higher levels of Aβ1-40 than APP Tg2576 mice, but they do not develop Aβ deposits even by 24 mo of age. BRI-Aβ42, which showed 5-10 fold lower transgene expression than BRI-Aβ40 develop florid parenchymal and cerebrovascular Aβ deposits by 3 mo of age in cerebellum and by 12 mo in forebrain. Changing Aβ42/Aβ40 levels in APP transgenic mice through crossing APP Tg2576 mice with BRI-Aβ mice inhibited amyloid pathology in BRI-Aβ40×Tg2576 mice, but significantly augmented deposition of amyloid in BRI-Aβ42×Tg2576. Behavioural evaluation of mice did not reveal any abnormalities in locomotor activity and motivation to explore novel environment. Furthermore, cognitive

evaluation of the mice revealed that both explicit spatial reference memory evaluated in a water maze and implicit associative learning of taste aversion was not compromised in 14 -16 mo-old mice when the BRI-Aβ42 mice show extensive amyloid deposition. Amyloid load in the brain of BRI-Aβ42 mice was not associated with their cognitive performance, suggesting a dissociation between plaque number and cognition. Association between species of Aβ levels in the brain of BRI-Aβ and bigenic BRI-Aβ×APP mice and memory indices will be presented and discussed. Mayo Clinic Jacksonville, Department of Neuroscience, 4500 San Pablo Rd. Jacksonville, Florida 32224 USA. This work was supported by Mayo Clinic Alzheimer's Disease Research Center.

QTL ANALYSIS IN BXD RI MICE SUGGESTS COMMON REGULATORY GENES FOR BRAIN IRON, COPPER AND ZINC

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Iron, copper, and zinc are vital for brain function yet toxic in excess. Thus, tight regulation of these metals is required, however the mechanism of regulation is poorly understood. We recently performed QTL analyses of regional brain content of these metals in 15 BXD recombinant inbred (RI) strains of mice. Large interstrain variations were observed in the content of each metal. Interestingly, within-strain covariation among the three metals was also observed, suggesting common genes may be involved in their regulation. Indeed, our analysis revealed a QTL on chromosome 17 (marker D17Mit49) strongly associated with all three metals. This QTL is also associated with ethanol acceptance, seizure susceptibility, and immune function. We report these and other phenotypic associations with this QTL, including gene expression clusters, and discuss candidate genes. This work contributes to understanding trace metal regulation as well as the relationship among iron, copper, zinc and related pathophysiology.Neuroscience Graduate Program, The Pennsylvania State University, State College, Pennsylvania USA. This work was supported in part by USPHS grants NS 35088 and AG 21190.

HYPOLOCOMOTION, ANXIETY, AND SEROTONIN SYNDROME-LIKE BEHAVIOUR CONTRIBUTE TO COMPLEX PHENOTYPE OF SEROTONIN TRANSPORTER KNOCKOUT MICE

AV KALUEFF, MA FOX, P GALLAGHER, DL MURPHY

Generated in LCS in 1998, serotonin transporter (SERT) knockout (-/-) mice have been assessed extensively worldwide in various behavioural tests. Although these well-studied mice are generally considered to be a genetic model of serotonin-related anxiety and depression, their complex behavioural phenotype is not yet fully understood. Here we assess in detail the behaviour of adult wild type (+/+), heterozygous (+/-) and -/- female mice (n = 7-8 per group; isogenic C57BL/6J background), subjected to a battery of behavioural paradigms. Overall, there were no differences in the novel odor/object finding test, nest-building, self-grooming (activity + sequencing), horizontal rod balancing and open field ethograms, indicating that in the SERT -/- mouse, major sensory functions, motor coordination and behavioural sequencing are normal. In contrast, there were striking reductions of all behaviours (especially vertical rears) in novelty-based tests (open field, novel object, sticky paper, social interaction), suggesting that both hypolocomotion and anxiety (rather than purely anxiety) influence the SERT -/- behavioural phenotype. In addition, these mice tend to move close to the ground, frequently display Straub tail, ticing/tremor and backward gaiting – the phenotype generally consistent with "serotonin syndrome"-like behaviour. The latter is in line with our knowledge of overall serotonin system hyper-function in these mice, and may represent a third factor determining their behavioural profile. Therefore, the behavioural phenotype of SERT -/- mice may be a result of their low activity + high anxiety + "serotonin syndrome"-like state. Understanding of the emerging complexity of SERT -/- mouse behaviour is crucial for a detailed dissection of their phenotype and for developing further neurobehavioural models using these mice.Laboratory of Clinical Science (LCS), National Institute of Mental Health, Bethesda, USA.

EVIDENCE FOR A COMMON QUANTITATIVE TRAIT LOCUS ON CHROMOSOME 9 FOR ACUTE COCAINE-, ETHANOL-, AND METHAMPHETAMINE-INDUCED STIMULATION

HM KAMENS[1,2], N LI[1,2], CS MCKINNON[1,2], TJ PHILLIPS[1,2,3]

Cocaine, ethanol, and methamphetamine are widely used addictive drugs that share the ability to produce locomotor stimulation in mice. In some animal models, a genetic correlation has been observed between sensitivities to the locomotor stimulant effects of these three drugs. Quantitative trait locus (QTL) mapping provided evidence that a gene(s) may reside on distal chromosome 9 that accounts for some of the phenotypic variance in the locomotor response to these drugs. In the current studies, a pair of reciprocal congenic mouse strains derived from the DBA/2J (D2) and C57BL/6J (B6) strains were used to confirm this gene. D2 mice stimulated more to an acute injection of ethanol, cocaine, and methamphetamine than did the D2.B6 congenic mice that possess a segment on chromosome 9 from 9 – 71 cM from the B6 strain. The reciprocal congenic strain (B6.D2) that has the 9 – 58 cM region of chromosome 9 from the D2 strain on a B6 background were more stimulated by cocaine and methamphetamine compared to B6 mice; however, these strains did not differ in response to ethanol. This response appears to be dependent upon sex only for the acute response to cocaine. These results confirm the presence of a QTL on chromosome 9 that is responsible for some phenotypic variation in the acute locomotor response to cocaine, ethanol, and methamphetamine. It is possible that a single gene may have pleiotropic effects on the locomotor response to all three drugs. [1] Department of Behavioral Neuroscience, [2]Portland Alcohol Research Center, [3]Veterans Affairs Medical Center, Oregon Health & Science University, Portland, Oregon USA. Supported by Department of Veterans Affairs, NIAAA P50 AA10760, F31 AA015822, and the N.L. Tartar Trust Fund.

STRESS-RELATED BRHAVIORAL RESPONSES IN MICE LACKING DOPAMINE D2 RECEPTORS

E-Y KANG, Sung Y KIM, Sa Y KIM, MS CHANG, J-H BAIK

Dopamine system is accelerated with the sympathetic nerve activation by stress such as emotional and environmental changes. Stress increases the neurochemical activity of dopaminergic neurons. We investigated the stress-related behavioral responses in mice lacking dopamine D2 receptor(D2R-/-) to examine the role of dopamine D2R in dopamine-mediated neural stress circuit. In this study, we observed that upon immobilization stress, the percentage of time-spent and the percentage of entries in the open arms were decreased in D2R-/- mice as compared to their WT littermates in the elevated plus maze(EPM) test. In the forced swimming test(FST) performed after chronic stress, the immobility time was increased in D2R-/- mice as compared to WT mice. Therefore, dopamine D2R-/- mice show an increased sensitivity and anxiety to stress than WT mice. Future studies, such as comparative researches on gene expression profiling after physical stress will allow us to identify the potential target in dopamine-mediated neural stress circuit.

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BDNF-INDUCED SYNAPTIC CHANGES IN THE MOUSE LACKING THE α_{1B} SUBUNIT OF N-TYPE CA2+ CHANNELS

D JEON, C KIM, YM YANG, H RHIM, E YIM, U OH, H-S SHIN

Brain-derived neurotrophic factor (BDNF) released by Ca2+ influx via N-type Ca2+ channels modulates activity-dependent synaptic plasticity in the hippocampus. However, the mechanisms underlying BDNF-induced synaptic enhancement remain elusive. Here we examined BDNF-induced synaptic changes at hippocampal CA3-CA1 synapses in the mouse lacking the α_{1B} subunit of N-type Ca2+ channels. BDNF-induced facilitation of the frequency of miniature excitatory postsynaptic currents (mEPSC) and BDNF-induced synaptic potentiation were reduced in the mutant. Furthermore, the presynaptic component of long-term potentiation (LTP), specifically driven by BDNF, was decreased in the mutant. Interestingly, P/Q-type Ca2+ channels had no significant contribution to these BDNF-induced presynaptic enhancements. In addition, we found that the mutant mice exhibited severe impairments in hippocampus-dependent learning and memory, especially in the long-term memory. Taken together, these result s

suggest that a positive feedback interaction between N-type Ca2+ channels and BDNF seems to be involved in the presynaptic enhancement and normal hippocampus-dependent learning and memory. Sensory Research Center, CRI, Seoul National University, Kwanak, Shinlim 9-dong, Seoul 151-742, KOREA. National Creative Research Initiatives of the Ministry of Science and Technology of Korea and Chemoinformatics Project of the Korea Institute of Science and Technology, Seoul KOREA.

COMBINING BEHAVIOR WITH *in vivo* NEURAL IMAGING TO STUDY PLASTICITY IN THE *C. elegans* TOUCH CIRCUIT

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The *C. elegans* touch circuit has been shown to undergo habituation, a simple form of non-associative learning and memory that that allows organisms to ignore irrelevant, repeated stimulation (Rankin et al 1990). In response to a non-localized tap to the culture plate, the *C. elegans* touch neurons are activated. The initial response is a reversal; following repeated tap stimulation, there is a decrease in both reversal rate and reversal distance. Previously we showed that a D1-like dopamine receptor DOP-1, and dopamine deficient mutant, cat-2 habituated faster than wildtype animals and that this effect may be acting at the level of the sensory neurons (Sanyal et al, 2004). Preliminary results indicate that Gq-alpha (egl-30) is the effector of DOP-1 in tap habituation, as egl-30 loss of function mutants show a precocious habituation phenotype similar to dop-1 mutants. Similar results were seen in pkc-1 mutants, suggesting a possible signaling pathway in the sensory neurons. We are currently using the genetically encoded FRET based calcium sensor, cameleon to examine the effects of dop-1, egl-30 and pkc-1 on the mechanosensory response of the touch receptor neurons. After repeated stimulation, our results suggest that the touch neurons of these mutants adapt faster than wildtype. In addition to cameleon, we have begun using another FRET based sensor, CKAR (Violin et al 2003), which measures PKC activity. We are currently characterizing PKC response to touch in wildtype, egl-30, dop-1 and pkc-1 mutant backgrounds. Together, these experiments will address key unanswered questions regarding the molecular mechanisms of neural plasticity in *C. elegans*, and are likely to provide insight into parallel processes in vertebrates. Division of Biological Sciences, University of California-San Diego, La Jolla, California USA. Funding support: NIH-NINDS 1 F31 NS051986-01.

MONOAMINE OXIDASE A AND SEROTONIN TRANSPORTER HAPLOTYPE INFLUENCES EMOTION REGULATION IN RESPONSE TO MATERNAL SEPARATION IN INFANT RHESUS MACAQUES

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Functional polymorphism in the regulatory regions of genes associated with neural monoaminergic function has been linked with monoamine utilization, neural activation, and consequent behavior. We investigated the association between infant rhesus macaque emotion regulation and two candidate gene promoter polymorphisms upstream of monoamine oxidase A (rhMAO-A-LPR) and serotonin transporter (rh5-HTTLPR) genes. Responses to a variety of novel situations/events were recorded in infant rhesus macaques 3-4 months of age (N=469) during a 24-hour separation from mothers and/or social groups and a composite score of emotional reactivity was calculated. Rh5-HTTLPR and rhMAO-A-LPR genotypes were categorized based on previously established transcriptional activity levels (rhMAOA-LPR: high, low and high/low heterozygous activity groups; rh-5-HTTLPR: high and low activity groups). Contrasts among haplotypes were computed using quantitative genetics software which incorporates pedigree analysis. Haplotypes differed in their association with measures of emotional reactivity. Hetero- or homozygosity for high activity alleles, when paired with a high activity rh5-HTTLPR genotype, is associated with the lowest emotional reactivity of all haplotypes ($p < .05$). High or low activity rhMAO-A-LPR genotype, when paired with a low activity rh5-HTTLPR genotype, resulted in the highest levels of emotional reactivity (all $p < .05$). There were no sex differences in any behavioral measure. These results suggest that serotonin pathway polymorphisms act cooperatively in their association with emotion regulation in infant rhesus macaques. University of California- Davis, Davis, California USA.

MODULATION OF THE NEURAL CIRCUIT BY INSULIN-LIKE SIGNALING FOR ASSOCIATIVE LEARNING IN *C. elegans*

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C. elegans shows an ability to associate cultivation temperature with feeding state. Well-fed animals migrate to and starved animals avoid from the cultivation temperature on a temperature gradient. Mutation in *ins-1* encoding the homologue of human insulin caused defective temperature-starvation associative learning, mutations in *daf-2* and *age-1* encoding the homologues of insulin/IGF-1 receptor and PI 3-kinase, respectively, partially suppressed the learning defect of ins-1 mutants, and the mutation in *daf-16* encoding forkhead-type transcriptional factor caused the weak learning defect. These results suggest that INS-1 antagonizes DAF-2 insulin-like signaling for associative learning between temperature and starvation. Interestingly, *age-1* animals associate their cultivation temperature with starvation quicker than wild type animals. This learning defect of *age-1* mutants was rescued by expressing AGE-1 in either one of three head interneurons, AIY, AIZ or RIA. Importantly, these three interneurons constitute the fundamental neural circuit for thermotaxis. We monitored the physiological activity of AIZ in response to changes in temperature and feeding state by using a genetically encoded calcium indicator. The activity of AIZ was down-regulated in starved wild type animals as compared to well-fed wild type animals. The AIZ activity of starved *ins-1* mutant however was not down-regulated. Our results suggest that insulin-like signaling modulates neuronal activity of thermotaxis interneurons during associative learning.[1]Division of Biological Science, Graduate School of Science, [2]Institute for Advanced Research, Nagoya University, Nagoya JAPAN[3]Molecular Genetics Research Laboratory, The University of Tokyo, Tokyo JAPAN [4]Present address: University of Texas Health Science Center at Houston, Department of Microbiology and Molecular Genetics, Houston, Texas USA [5]Present address: Structural Biology Center, National Institute of Genetics, Mishima JAPAN

BEHAVIORAL CHARACTERIZATION OF CHROMOSOME SUBSTITUTION STRAINS USING A COMPLEX BEHAVIORAL TEST

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The modified hole board (mHB), which is a complex behavioral test for rodents, allows us to assess for a variety of different motivational systems in parallel (i.e. exploration, locomotion, avoidance, arousal). This approach is essential for behavioural characterization since the motivational system of interest is strongly influenced by other behavioural systems. In previous experiments the C57BL/6J and A/J mouse inbred strains were behaviorally phenotyped in the mHB and showed differences in almost all motivational systems. To elucidate the genetic mechanisms underlying those behavioral differences, we performed further analyses with a commercially available set of mouse chromosome substitution (CS) strains. For this set C57BL/6J is the host strain and A/J is the donor strain. We identified one CS-strain that differed in only avoidance behavior (i.e. anxiety) from the C57BL/6J, but not in any other of the motivational systems. To identify which of the genomic regions that the CS-strain inherited from the A/J are responsible for this phenotype, an F2-intercross between C57BL/6J and the CS-strain is currently produced. After quantitative trait loci analyses we hope to identify candidate genes and future work will be directed towards use of knockout strategies and micro-array analyses to assess the contribution of these candidate genes in relation to anxiety-related behavior. Utrecht University, Utrecht, THE NETHERLANDS.

DIFFERENCES IN ACQUISITION AND EXTINCTION OF FEAR BETWEEN C57BL/6 AND DBA/2 MICE AFTER EXTENSIVE CONDITIONING

KM LATTAL, DK DUFFIELD

Behavioral and neurobiological studies of inbred and genetically modified mice have identified a number of neural systems and signal transduction molecules involved in the formation of long-term contextual memories. An issue of important theoretical and clinical interest is understanding the neurobiological mechanisms that occur during fear extinction, in which animals learn that the associative relation between the context and the shock established during initial acquisition has been severed. Extinction is

an active process that suppresses the original memory without affecting the content of that memory. A major challenge for the genetic study of extinction is that differences in learning during fear conditioning often preclude the behavioral study of extinction because inbred strains of mice (such as DBA/2 and C57BL/6) show differences in amount of initial conditioning. In several experiments, we examine the effects of different conditioning protocols to overcome deficits in acquisition. We show deficits in DBA/2 compared to C57BL/6 mice in acquisition of contextual fear, but when performance is brought to common levels after extensive conditioning, DBA/2 mice show enhancements in the development and long-term maintenance of extinction. These findings are consistent with others showing that manipulations impair acquisition may facilitate extinction. Theoretical and clinical implications will be presented. Department of Behavioral Neuroscience, Oregon Health & Science University, Portland Oregon USA 97239.

ALTERED SPINDLE OSCILLATIONS IN MICE LACKING α1G SUBUNIT OF T-TYPE Ca^{2+} CHANNELS

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Spindle oscillations (6-15 Hz) are generated by thalamocortical network properties. The rebound burst firings are generated in thalamocortical relay (TC) neurons at the outset of rhythmic GABAergic IPSPs imposed by thalamic reticular (RE) neurons, and transferred to cortical neurons which induce rhythmic EPSPs, the origin of cortical EEG spindle waves. We previously showed that rebound burst firings in TC neurons were absent in mice lacking α1G T-type Ca^{2+} channels. However, we also observed spindle-like waves (6-14Hz) in cortical EEG of mutant mice during NREM sleep. To verify this finding, we closely investigated spindle oscillations under barbiturate anesthesia. Barbiturate (20mg.kg, i.p.) provoked typical waxing and waning spindle waves (6-14 Hz) in the wild-type. Mutants also exhibited spindle waves in cortical EEG under the anesthesia. However, the amplitude and the duration of spindles induced by barbiturate were decreased in mutants compared to those in the wild-type. In addition, the focal EEG recorded in TC region showed oscillatory patterns synchronized to cortical spindles in both genotypes under the anesthesia. The present findings suggest that α1G subunit of T-type Ca^{2+} channels is not essential for the generation and propagation of spindles between the thalamus and the cortex, but required for the maintenance of the strength of the waves. To elucidate the mechanism of spindle oscillations without rebound burst firings, firing properties in TC and RE neurons during spindle oscillations will be characterized in further experiments. [1]Center for Neural Science, Division of Life Sciences, Korea Institute of Science and Technology, Seoul, KOREA, 136-791, [2]Department of Neuroscience, University of Science and Technology, Daejeon KOREA 305-333. This work was supported by Chemoinformatics Program of Korea Institute of Science and Technology (Grant No. 2E18790).

BEHAVIORAL PHENOTYPING OF A MURINE AD-MODEL IN A SEMI-NATURALISTIC ENVIRONMENT

L LEWEJOHANN, N REEFMANN, P WIDMANN, N SACHSER

Transgenic mice are usually housed singly or in unisexual groups in small barren cages. Such restricted environments prevent the mice from showing a variety of species-specific behavior and consequently constrain behavioral phenotyping. The aim of this project is to characterize TgCRND8-mice carrying a genetic disposition to develop Alzheimer-like pathology and their wild-type conspecifics in a semi-naturalistic environment (SNE). The SNE measures 1.75 by 1.75 by 2.1m (L x W x H) and contains several floors connected by small bridges and ropes. The population was allowed to grow to a size of 40 individually marked adult mice. Behavioral observations were conducted at 30 and 60 days of age (pre-plaque phase) and at 120 and 150 days of age (plaque-phase) by trained experimenters. Up to 55 unique behavioral patterns from various behavioral domains were differentiated. The mice established a complex social structure comprising several territories. First results reveal surprisingly little significant differences between genotypes that were true at all ages and for both sexes. However, analysis of social interaction patterns and population dynamics indicates that the mice themselves can distinguish between different genotypes. Institute of Neuro and Behavioral Biology, University of Muenster, Muenster GERMANY.

THE AMPAKINE CX546 RESTORES THE PREPULSE INHIBITION AND LATENT INHIBITION DEFICITS IN mGluR5 MICE

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In order to test the possible role of mGluR5 in the behavioral endophenotypes shared with schizophrenia and other psychiatric disorders, we used genetic engineering to create mice carrying null mutations in this gene. We how here for the first time, that compared to their mGluR5+/+ littermates, mGluR5-/- mice has disrupted latent inhibition (LI), measured in a thirst-motivated conditioned emotional response procedure by comparing suppression of drinking in response to a noise in mice which previously received 0 (non-preexposed) or 40 noise preexposures (preexposed) followed by 2 noise-foot shock pairings. Administration of the modulator of a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR), CX546, during only the conditioning phase improved the disrupted LI in mGluR5-/- mice to normal level and facilitated LI in control C57BL/6J mice with extended number of conditioning trails (4 noise-shock pairings). We confirm the work of others that Prepulse Inhibition (PPI) is impaired in mGluR5-/- mice to a level that could not be further impaired by antagonist of N-methyl-d-asparate receptors (NMDAR) – MK-801, and go on to show rescue with CX546, but not aniracetam. This provides evidence that direct modulators of AMPAR can elicit antipsychotic action and represent a new pathway for treatment of schizophrenia. [1]Samuel Lunenfeld Research Institute, Toronto, CANADA, [2]Program in Neuroscience University of Toronto, CANADA. This work was supported by the Ontario Mental Health Foundation (OMHF).

DISENTANGING BEHAVIORAL PHENOTYPES OF INBRED MOUSE STRAINS CORRELATED WITH SPECIFIC GENE CLUSTERS

M LOOS, AB SMIT, S SPIJKER

Various inbred mouse strains differ in anxiety and attention related behavior due to genetic polymorphisms. Hovatta (Hovatta et. al., 2005) showed that strain differences in anxiety-related behavior can be functionally related to gene expression differences. Using a test-battery of anxiety and attention test, we dissected these multi-component behaviors into behavior parameters that probe the different underlying components (e.g. motivation, locomotor activity). Subsequently we investigated whether these disentangled behavioral components have specific gene expression correlates.

We measured the behavior of six inbred mouse strains (129S6/SvEvTac, A/J, C3H/HeJ, C57BL6/J, DBA/2J and FVB/NJ) in eight different ethologically relevant exploration and hypophagia anxiety tests, as well as in the 5-choice serial reaction time test (5CSRTT) to measure attention. Interestingly, strains that show low levels of anxiety at one parameter (e.g. C57BL6/J, time spend in middle of open field) can show high levels of anxiety at other parameters (e.g. C57BL6/J, time spend exploring a novel object). This signifies that multiple ethologically relevant tests are necessary to disentangle complex behaviors, and hence to determine their specific genetic encoding. From the tests, we clustered multiple behavioral parameters to retrieve similar behavioral components across different genetic backgrounds. In addition, we retrieved the GEO-dataset from these 6 strains (Hovatta et. al., 2005), and correlated gene expression with clusters of behavioral parameters. This may indicate that specific genetic polymorphisms, by virtue of distinct gene expression profiles, translate into different modalities of behavioral output.

Reference: Hovatta I, Tennant RS, Helton R, Marr RA, Singer O, Redwine JM, Ellison JA, Schadt EE, Verma IM, Lockhart DJ, Barlow C. Glyoxalase 1 and glutathione reductase 1 regulate anxiety in mice. Nature, 2005 Dec 1;438(7068):662-6. Department of Molecular and Cellular Neurobiology, Center for Neurogenomics and Cognitive Research, Vrije Universiteit, Amsterdam THE NETHERLANDS.

COGNITIVE DEFICITS IN THE R6/2 MOUSE MODEL OF HUNTINGTON'S DISEASE

E LUDVIG, H HERMAN, G DILLON, B ALLEN, J GOODMAN, J MURPHY, B ZAHASKY, M PECK, L MENALLED, D BRUNNER

The R6/2 transgenic mouse is one of the most popular mouse models for Huntington's disease (HD). This mouse model is transgenic for the human huntingtin (htt) gene with 120-150 CAG repeats. R6/2 mice show decreased survival and gross motor deficits beginning as early as 5 weeks of age and cognitive impairment in both spatial learning and visual discrimination tasks. In this study, mice were

tested from 4 to 12 weeks of age on a full battery of cognitive tests, including novel object recognition, context and cued fear conditioning, spatial learning in the holeboard, social transmission of food preference, two-odor discrimination and reversal, and y-maze alternation. The most pronounced and robust deficits for the transgenic mice occurred in the novel object recognition task with a 4-hour train-test delay and the working memory measures in the holeboard. This series of tests provides a coherent cognitive testing battery suitable for high-throughput drug screening with R6/2 mice. Psychogenics Inc, Tarrytown, New York USA.

ANALYSIS OF 100 STUDIES OF C57BL/6 MICE IN THE MORRIS WATER MAZE: DO TASK PARAMETERS MAKE A DIFFERENCE?
E MARCOTTE, D WAHLSTEN

The Morris submerged platform water escape task has become the most widely used method to assess spatial learning and memory in mice. One remarkable feature of the large literature on this task is the wide range of results obtained in different laboratories. We also found that different labs almost always employ a different set of task parameters. We investigated relations between task parameters and two measures of learning and memory - latency reduction over trials and percent time in the correct quadrant on probe trials. The genetic variable was controlled by limiting the analysis to the C57BL/6 inbred strain that was often employed as a wild-type strain in studies of targeted mutations and was always included in multiple strain comparisons. More than 20 animal and task parameters were assessed from published descriptions, including substrain, age, sex, number of training trials, time on platform, water tank size, relative platform size and depth below the surface, water temperature and opacity, and Illumination. Hierarchical multiple regression analysis was used to identify an array of variables that provided the best account of variation in results. Department of Biological Sciences and Great Lakes Institute, University of Windsor, Windsor, Ontario, CANADA N9B3P4. This work was supported by NIAAA and NSERC.

THREE MURINE ANXIETY MODELS: RESULTS FROM INBRED STRAIN COMPARISONS
LC MILNER[1], JC CRABBE[1,2]

Testing rodents in a variety of behavioral assays designed to detect anxiety-like behaviors is often used, both to predict pharmacological therapies for anxiety disorders and to determine hereditary factors contributing to these disorders. However, the literature surrounding rodent models is discrepant concerning which variables within these models reflect anxiety-like behavior distinct from general activity and whether these assays are measuring the same underlying construct. The goals of the current experiment were to test a large number of inbred mouse strains in three different tasks commonly used in anxiety research in order to examine the genetic contributions to behavior in these assays and to determine which responses were correlated across tasks. Mice from 15 inbred strains were sequentially exposed to three different tasks: the light/dark box, the elevated zero-maze and the open field. Variables used to index both anxiety-like behavior and locomotion were recorded. Significant strain differences, ergo hereditary contributions, were found for almost all variables measured, which is in agreement with earlier studies. Principal components analyses performed on the data showed that variables associated with both locomotor activity and anxiety-like behaviors loaded onto the first factor, while urine and defecation indices loaded onto the second factor. The results of our principal components analyses differ from previous research because our analysis suggests that general activity measures and anxiety are linked. Therefore, although these tasks appear to assess similar behavior, they may not be measuring anxiety-like behaviors exclusively. [1]Department of Behavioral Neuroscience, Oregon Health & Science University, and [2]Deparment of Veterans Affairs, Portland, Oregon USA. This work was supported by grants T32AA07468, AA10760 and AA13519 from the National Institutes of Health, and by a grant from the Department of Veterans Affairs.

CASEIN KINASE 1 EPSILON (*Csnk1e*) IS A CANDIDATE GENE FOR STIMULANT SENSITIVITY IN MICE AND HUMANS

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The genetic predisposition towards drug abuse may be influenced by genetic differences in the sensitivity to the effects of drugs. In an effort to identify genes that influence sensitivity to methamphetamine (MA), we selectively bred mice for high (HMACT) or low (LMACT) MA-induced locomotor activity and used them to identify quantitative trait loci (QTL) for this phenotype. We also measured gene expression in the nucleus accumbens of drug-naïve male HMACT and LMACT mice using Affymetrix microarrays. Statistically significant expression differences were identified for several genes, including *Csnk1e*. *Csnk1e* is known to phosphorylate Darpp-32, which is critical for the locomotor response to stimulant drugs. We identified an expression QTL (eQTL) for *Csnk1e* on chromosome 15 that co-mapped with one of the QTLs for the MA sensitivity, suggested the existence of an allele that influences MA sensitivity by altering expression of *Csnk1e*. We also conducted a parallel study to determine whether polymorphisms in *Csnk1e* influenced sensitivity to amphetamine in humans. One hundred healthy human volunteers were administered d-amphetamine (0, 10 and 20 mg) in a double-blind, counterbalanced order. Subjects with one or two copies of the C allele of rs135745 were more sensitive to the 10 mg dose of amphetamine on the Drug Effects Questionnaire (p=0.001), and on the "euphoria" scale of the Addiction Research Center Inventory (p=0.009). [1] Department of Human Genetics, University of Chicago, Chicago, Illinois USA [2] Department of Psychiatry, University of Illinois at Chicago, Chicago, Illinois USA[3] Department of Psychiatry, Columbia University, New York, New York USA [4] Department of Psychiatry, University of Chicago, Chicago, Illinois USA [5] Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, Oregon USA This work was supported by MH70933, DA10913, DA02812, RR00055, AA07468, NARSAD, and a grant from the Department of Veterans' Affairs.

SOCIAL REWARD IN JUVENILE MICE IS A HERITABLE PHENOTYPE

Jules PANKSEPP, K JOCHMAN, G LAHVIS

Mouse models are important tools for elucidating relationships between genetic variation and the organization of complex behavioral phenotypes. In particular, we have developed a strategy for probing domains of social function in juvenile mice, and with this have carried out an initial behavioral screen of some common inbred strains (A/J, BALB/c, C57BL/6 and DBA/2). Here we present our findings, with a specific focus on the BALB/c and C57BL/6 strains, using 3 novel tests of juvenile mouse social behavior—Resident-Intruder, Social Conditioned Place Preference and Social Gauntlet. Consistent with some other studies, we found that in each test juvenile C57BL/6 mice exhibit a preponderance of social approach behaviors compared to BALB/c. The reduced social tendencies of juvenile BALB/c mice were not attributable to differences in locomotor activity, the capacity for motivated behavior, contextual learning or 'generalized' anxiety. Furthermore, possible explanatory variables, such as sexual motivation, maternal care and the genetic identity of the 'stimulus' mouse, did not account for the strain differences. Strain-specific genetic variation thus moderates the social approach phenotypes of juvenile mice. Taken together, the social behaviors of juvenile C57BL/6 mice are consistent with several formulations of reward theory. As such, juvenile social reward is a tractable phenotype for forward genetic approaches in mice. mUniversity of Wisconsin – Madison, Madison, Wisconsin USA. Funding Support: NIH NRSA GM07507 (J.B.P) and NIH R03 HD046716 (G.P.L.)

GENETIC DIFFERENCES IN THE EFFECTS OF ACUTE AND CHRONIC FORCED SWIM STRESS ON SENSITIVITY TO ETHANOL-INDUCED LOSS OF RIGHTING REFLEX IN INBRED MICE

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Individual differences in stress responsivity as well as in sensitivity to ethanol are in part, genetically mediated. The availability of inbred strains of mice offers excellent model systems in which to examine the genetics of ethanol and stress related behavioral phenotypes. In the present experiment, DBA/2J, C57BL/6J (males only), ILS, ISS and their F1 hybrids (males and females) were subjected to one 10-minute session of forced swimming (acute stress); or fourteen consecutive days of 10-minute forced

swimming sessions (chronic stress). Animals received a 4.1 g/kg intraperitoneal injection of ethanol 24 hours following the final swim session and duration of LORE was compared to unstressed ethanol-injected littermates. Duration of LORE was defined as time between loss and recovery of the righting reflex. In the DBA/2J and C57BL/6 males, only C57BL/6 mice displayed increased sensitivity to alcohol after 14 days of forced swimming ($F_{2, 26} = 7.6$; $p = .003$). In the ILS, ISS and F1s, a three-way ANOVA showed main effects for sex ($F_{1, 144} = 27.19$; $p << .0001$), strain ($F_{2, 144} = 617.1$; $p << .0001$) and for condition ($F_{2, 144} = 23.76$; $p << .0001$) on duration of LORE. Additionally, there was an interaction between sex and strain ($F_{2, 144} = 3.73$; $p = .03$) and strain and condition ($F_{4, 144} = 2.96$; $p = .02$) with ISS and F1 males and females and ILS males only displaying increased sensitivity to ethanol following fourteen, but not one day of restraint stress. These results suggest that genetics and exposure to chronic stress may interact to produce differential effects on ethanol sensitivity in inbred strains of mice. [1]Center for Neuroscience, University of Colorado, Boulder Colorado USA; [2]Institute for Behavioral Genetics, University of Colorado, Boulder Colorado USA; [3]Department of Psychology, University of Colorado, Boulder Colorado USA; [4]Section on Behavioral Science and Genetics, NIAAA NIH USA; [5]Department of Integrative Physiology, University of Colorado, Boulder, Colorado, USA. This work was supported by NIH grant DA017637.

REMOTE EFFECTS OF EARLY TREATMENTS IN MOUSE AND RAT BEHAVIOR DEPEND ON GENOTYPE

NV MARKINA, OV PEREPELKINA, OS BOYARSHINOVA, II POLETAEVA

Perinatal treatment of rats and mice (pain stimulation, drug injections) induced changes in the normal CNS development, which are not possible to reveal in neonates or adolescent animals. At the same time The behavioral testing in the adult stage (with test battery) make it possible to reveal the number of differences from controls, their span and direction being different in animals of different genotypes. C57BL, CBA, C3H, DBA/2, 101/HY mice as well as Wistar, WAG/Rij and KM rats were used. The set of data will be presented which demonstrate the genotype dependency in the remote effects of early injections of ACTH 4-10 fragment, its stable synthetic analogue Semax, buspirone et al. Rat and mouse scores in audiogenic epilepsy, behavioral traits, revealed in the open-field and in cross-maze as well as in pain thresholds show strain specificity in adult animals as reactions to early treatments (first week of life). As the example - the tail-flick thresholds (pain sensitivity) in the 2-3 months old mice were were significantly lower in saline treated mice in comparison to intact and Semax treated animals. The number of tyrosine-hydroxilase containing neurons in *zona inserta* was significantly higher than in controls after ACTH 4-10 fragment and lower – after Semax neonatal treatments. The strain specificity in the effects of early treatments could be revealed as significant (although not large) differences in the behavioral indices of adult animals. This issue is important for behavioral terathology, and in brain and behavior development study. Biology faculty, Moscow State University, Moscow RUSSIA. Partly supported by RBNF (N 04-04-48445) and IB74BO-111081.

USING PUBLIC GENE EXPRESSION DATABASES TO DEFINE TRANSCRIPTIONAL PATTERNS OF NEUROADAPTATION TO ETHANOL WITH CELLULAR RESOLUTION

I PONOMAREV, KH LODOWSKI, RA HARRIS, SE BERGESON

Gene expression databases that characterize transcriptional fingerprints of individual cell types recently became available. An approach that combines the sensitivity of whole tissue microarrays with the specificity of single cell transcriptomes can now be used to define transcriptional patterns of brain functions with cellular resolution. We used cDNA microarrays to investigate cellular responses to ethanol in C57Bl/6 (B6) and DBA/2 (D2) inbred mouse strains which show marked differences on several ethanol-related phenotypes. Transcriptional profiles were examined in cerebral cortex of B6 and D2 mice after a single dose of ethanol (4 g/kg, 20% v/v, ip). Alcohol administration resulted in regulation of largely different pools of genes in B6 and D2 animals, suggesting differential effects of genetic polymorphism on molecular mechanisms of cellular adaptation to ethanol. We used the Mouse Neuronal Expression Database (http://mouse.bio.brandeis.edu) to identify subsets of transcripts enriched in excitatory and inhibitory neurons as well as glial cells, providing evidence for cellular plasticity in individual cell types. A

quantitative assessment of a combined data set revealed that distribution of ethanol-regulated transcripts across different neuronal populations significantly deviated from chance, suggesting differential effects of ethanol on different neuron types in cerebral cortex. Furthermore, relative frequencies of transcripts enriched in different cell types differed between B6 and D2 strains, showing an under-representation in parvalbumin-positive GABA interneurons in D2 mice and an over-representation in cholecystokinin-positive GABA interneurons in B6 mice. Overall, results suggest that genetic differences between B6 and D2 mice underlie different requirements for molecular and cellular adaptation to alcohol, which may account for differences in ethanol-related behaviors.Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin, Austin, Texas USA. Supported by grants from National Institute of Alcohol Abuse and Alcoholism, NIH (AA UO1 13520, AA UO1 13518, AAUO1 13475; INIA Projects).

CRITICAL PERIODS FOR REVERSING THE EFFECTS OF MECHANOSENSORY DEPRIVATION IN *C. elegans*

S RAI, CH RANKIN

Sensory experience at different stages during development can alter varying structures and functions of the nervous system suggesting that the timing of the occurring experience is critical. Research on a variety of different organisms has shown that early deprivation of sensory experience has detrimental effects on nervous system development. In these studies we use the nematode *C. elegans* as a model organism to demonstrate the effects of deprivation of mechanosensory experience on behaviour and development, and to identify critical periods for reversing the detrimental effects of deprivation by introducing mechanosensory experience during development. Earlier studies have found that worms reared in isolation, without the mechanosensory stimulation from conspecifics, respond significantly less to a mechanical tap stimulus and are significantly shorter in body length than worms raised in age-matched colonies. A study of the synapse between the mechanosensory neurons and the command interneurons showed that in isolate-raised worms this synapse was weaker (fewer post synaptic glutamate receptors and fewer pre synaptic vesicles) than the synapses of worms raised in a colony condition. In this study, brief mechanical stimulation at any time during development reversed the effects of isolation on the behavioral response to tap and glutamate receptor expression suggesting there is no critical period for these two measures. In addition, stimulation early in development (during larval stage L1), but not later, rescues vesicle expression and stimulation during L1, L2 and L3 rescues the effects of isolation on body growth suggesting there is a critical period for these measures during L1 and L3 respectively. These results suggest different aspects of development will require varying amounts of stimuli at varying time points in development to fully rescue the effects of deprivation on the organism. With this simple model system we have the possibility of determining the cellular bases of such differences. University of British Columbia, Vancouver, British Columbia CANADA. Funded by operating grant from CIHR and HELP to C.H.R.

GENETIC AND FACTORIAL ANALYSIS OF BEHAVIORS RELATED TO ANXIETY, DEPRESSION, AND ALCOHOL INTAKE IN AN INTERCROSS BETWEEN LEWIS AND SHR RATS

A RAMOS, G IZIDIO, FB OLIVEIRA, FM SILVA, NEB MELO, APR COSTA

Epidemiological studies show significant comorbidity between anxiety, depression and alcohol abuse, which is supported by some but not all pre-clinical studies. The aim of the present study was to genetically analyze anxiety- and depression-related behaviors through an intercross between Lewis (LEW) and SHR rats and to investigate the relationship between these behaviors and alcohol intake in an F2 segregating population. Rats from four genotypic groups (LEW, SHR, F1, n=10/group/sex; F2, n=50/sex) were tested in the open field (OF), black/white box (BWB) and forced swim test (FST). Moreover, F2 animals were submitted to an ethanol self-administration protocol: forced (10%) or free-choice (2.5, 5, 10 and 20%) with each condition lasting two days. Heritability was estimated based on variances of all genotypic groups. These values were low/null for BWB variables but high for the OF (0.66 and 0.50 for inner locomotion of males and females, respectively) and FST (0.66 and 0.60 for time of immobility of males and females, respectively). A factor analysis revealed four factors for males and five for females. Measures of alcohol intake loaded on one single factor in males and on two factors (for low

or high concentrations) in females. In males there was a correlation between forced ethanol intake and anxiety- and depression-related behaviors. Differently from previous data, time of immobility in the FST was not related with inner locomotion in the OF, suggesting that an ongoing QTL analysis may not identify pleiotropic loci for anxiety- and depression- related behaviors. Departamento de Biologia Celular, Embriologia e Genética, Universidade Federal de Santa Catarina, Florianópolis, SC, BRAZIL. This work was supported by Fapesc/CNPq (Pronex 427/2003).

DIFFERENTIAL CONTRIBUTIONS OF DOPAMINE D1, D2, AND D3 RECEPTORS TO MDMA-INDUCED EFFECTS ON LOCOMOTOR BEHAVIOR PATTERNS

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MDMA (3,4-Methylenedioxymethamphetamine) is a psychoactive drug that has unusual and distinctive behavioral effects in both humans and animals. In rodents, MDMA administration produces a unique locomotor activity pattern, with high activity characterized by straight locomotor paths and perseverative thigmotaxis. Although considerable evidence supports a primary role for serotonin release in MDMA-induced locomotor activity, dopamine receptor antagonists have recently been shown to attenuate MDMA locomotor effects. Here we tested the hypothesis that dopamine D1, D2, and D3 receptors contribute to MDMA-induced alterations in locomotor activity and motor patterns. Dopamine D1, D2, or D3 receptor knockout (KO) and wild-type (WT) mice received vehicle or (+/-)-MDMA and were tested for 60 min in the behavioral pattern monitor. D1 KO mice exhibited significant increases in MDMA-induced hyperactivity during the late testing phase, as well as an overall increase in straight path movements. In contrast, D2 KO mice exhibited reductions in MDMA-induced hyperactivity in the late testing phase, and exhibited significantly less sensitivity to MDMA-induced circling behavior. At baseline, D2 KO mice exhibited reduced activity and more circumscribed movements compared to WT mice. Female D3 KO mice exhibited slightly reduced MDMA-induced hyperactivity. These results indicate differential modulatory roles for D1 and D2 and perhaps D3 receptors in MDMA-induced hyperactivity. More specifically, D1 receptor activation appears to modify the type of activity (linear vs. circumscribed) while D2 receptor activation appears to contribute to the repetitive thigmotaxis produced by MDMA administration.
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KNOWING YOUR BEHAVIOURAL MODEL: LCM-LongSAGE-Lite ESTABLISHED FOR THE DEVELOPING MOUSE BRAIN

Y-Y XIE, S BOHACEC, LLC LEE, A DELANEY, J KHATTRA, R HOLT, A SIDDIQUI, SJM JONES, MA MARRA, EM SIMPSON

The examination of differential gene expression from specific brain regions remains a critical challenge in developmental neuroscience. As part of a larger Genome Canada project, the 'Atlas of Gene Expression in Mouse Development', we are using Laser Capture Microdissection (LCM) and LongSAGE (Serial Analysis of Gene Expression) to examine differential expression from 66 brain regions from embryonic and adult mice. To overcome the limitations of reduced RNA quantity imposed by isolating specific regions, we used a modification of the SAGE-Lite procedure to amplify the starting sample. Here we report the establishment of LCM-LongSAGE-Lite for the brain that, for the first time, generates SAGE libraries with deep sequencing (>100,000 tags), from as little as 10 ng of high-quality LCM RNA. Furthermore, we demonstrate the use of this methodology to identify candidate genes differentially expressed between the embryonic ventricular/subventricular zones of the ventral and dorsal telencephalon. We conclude that LCM-LongSAGE-Lite is a robust and valid approach for global gene expression profiling of developing neuronal tissue.Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, British Columbia CANADA. Funding support was provided by Genome Canada and Genome British Columbia.

ANTI-DEPRESSION PHENOTYPE IN MANNOSIDE 6-β N-ACETYLGLUCOSAMINYL TRANSFERASE 5 (Mgat5)-DEFICIENT MICE

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The Central Nervous System (CNS) is rich in complex-type N-glycans, including the GlcNAc-branched N-glycans products of Golgi UDP-GlcNAc:N-acetylglucosaminyltransferases (Mgat1, Mgat2, Mgat4 and Mgat5). Most cell surface receptors are N-glycosylated, with further modification in the Golgi generating the GlcNAc-branched N-glycans, which bind to mammalian lectins. An Mgat1 deficiency is embryonic lethal demonstrating a requirement for N-glycans with a least one branch. Mgat2$^{-/-}$ mice mimic the defects of type 2 Congenital Disorders of Glycosylation (CDG) disease, including developmental and psychomotor abnormalities. Mice with a neuron-specific deletion of Mgat2 or a systemic deletion of Mgat5 appear normal at birth. However, altered behavioral traits in mice are revealed by well-designed behavioral paradigms. Here we have examined Mgat5 deficient mice in a battery of behavioral tests. Mgat5 $^{-/-}$ mice were normal for startle reactivity, sensori-motor gating, motor coordination and spatial learning but showed gender-dependent difference in anxiety level. Male and female Mgat5$^{-/-}$ mice showed a robust decrease in immobility time in the forced swim test and the tail suspension test. After chronic mild stress, Mgat5$^{-/-}$ mice displayed even further decreases in immobility, indicating a resistant-to-depression phenotype. Our results suggest a role for Mgat5 and the tetranntennary complex-type N-glycans in the pathogenesis of depression. [1] Institute of Medical Sciences, University of Toronto, Ontario CANADA[2] Department of Molecular & Medical Genetics, University of Toronto, Ontario CANADA[3] Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario CANADA.

INOSITOL MONOPHOSPHATASE MAINTAINS SUBCELLULAR COMPARTMENTATION OF INTERNEURONS AND REGULATES BEHAVIOR IN THE MATURE NERVOUS SYSTEM OF *C. elegans*

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C. elegans nervous system is composed of only 302 identifiable neurons whose synaptic connectivity is completely known from ultrastructural study. This simple nervous system, however, can generate wide range of behavior. One of those is thermotaxis behavior, in which *C. elegans* animals remember the ambient temperature and move to that temperature when placed on thermal gradient. An standout advantage of using thermotaxis behavior as a model system is the neural circuit composed mainly of five types of neurons (AFD, AWC, AIY, AIZ and RIA) which governs the behavior: this and other features of *C. elegans* nervous system give us an opportunity to dissect integratively the mechanism of behavior from genetic, cellular, network to individual level as in this study. From genetic screen, we isolated an athermotactic mutant ttx-7. ttx-7 is a sole *C. elegans* homolog of Lithium-sensitive enzyme Inositol Monophosphatase (IMPase), whose in vivo role was totally unknown despite of the much knowledge on its biochemical properties. We found that TTX-7 is necessary for maintenance of synaptic proteins' localization within RIA interneurons and thermotaxis behavior in adult stage. RIA interneuron is apparently monopolar with single neurite, but the presynaptic and postsynaptic compartments are clearly separated within the single neurite, which makes RIA an suitable model neuron to investigate the establishment and maintenance of subcellular compartments. Further characterization of compartmentation in RIA will lead to understanding in vivo role of IMPase, the mechanism and importance of compartmentation from the various aspects of genes, neurons and whole nervous system. [1]Department of Molecular Biology, Division of Biological Sciences, Graduate School of Science, Nagoya University, Nagoya JAPAN [2]Institute for Advanced Research, Nagoya University, Nagoya JAPAN [3]PRESTO, Japan Science and Technology Corporation.

LONG-TERM MEMORY IN C. ELEGANS IS SUBJECT TO RECONSOLIDATION

TA TIMBERS, JK ROSE, CH RANKIN

Memory for habituation in *C. elegans* is subject to reconsolidation (the theory that retrieval of a previously consolidated memory renders it, at least partially, to a labile state (Nader et al., 2000)) and further, this reconsolidation shares some of the same molecular mechanisms necessary for consolidation. Results show that long-term memory (LTM) for habituation lasts upwards of 48 hours and is not disrupted by

protein synthesis inhibition delivered 24 hours post training. However, if protein synthesis inhibition is given immediately after a reminder treatment (10 taps) this interferes with the memory; the animal responds to the tap stimulus at 48 hours as if it were a novel stimulus. From this it can be determined that reactivation of the memory prior to protein synthesis inhibition was required to interrupt memory reconsolidation. We are currently investigating the amount of reminder stimulation necessary to reactivate the previously consolidated memory for habituation in order for memory to be disrupted by reconsolidation blockade. Consolidation of LTM for habituation in *C. elegans* is dependent upon both the presence and activation of non-NMDA –type glutamate receptors. Results show that reconsolidation blockade shares a molecular mechanism with consolidation as it also requires non-NMDA-type glutamate receptors and a change in GLR-1 expression is noted following either phenomenon. We are currently testing a variety of genes including CREB and CRE responsive genes to further investigate whether more molecular mechanisms are also shared between consolidation and reconsolidation. Department of Psychology and Brain Research Centre, University of British Columbia, Vancouver, British Columbia C V6T 1Z4 CANADA. This work was supported by the Natural Sciences and Engineering Research Council of Canada.

REDUCING THE NUMBER OF ANIMALS USED IN BEHAVIORAL GENETIC EXPERIMENTS USING CHROMOSOME SUBSTITUTION STRAINS

MC LAARAKKER, F OHL, HA VAN LITH

Over the past decade, methods for genome analysis of animal models have been developed to identify and locate QTLs. Chromosome substitution strains (also called consomic lines or strains) can accelerate the identification and mapping of QTLs. Chromosome substitution strains are produced by transferring a single, full-length chromosome from one inbred strain – the donor strain – onto the genetic background of a second inbred strain – the host strain – by repeated backcrossing. Because the host and donor strain are genetically very diverse, the consomic panels can be used as a general genetic discovery tool. Therefore, panels of chromosome substitution strains are an advantage to researchers studying the genes affecting developmental, physiological and behavioral processes. The Division of Laboratory Animal Science, Utrecht University, is specifically interested in behavioral genetic research using a commercially available set of mouse chromosome substitution strains. Determination of the number of animals required per strain of both the host strain and the consomic strain for the genetic analyses is one of the most important and difficult decisions one has to make. Based on the results obtained from behavioral tests (i.e. the modified hole board test) with the two parental strains, the minimum number of animals from each of the host and consomic strains that are required for a successful behavioral genetic analysis can be estimated. Correct application of statistical knowledge can lead to a further reduction in the number of animals used in behavioral genetic experiments using chromosome substitution strains. Utrecht University, Utrecht, THE NETHERLANDS.