14th Annual Meeting of the International Behavioural and Neural Genetics Society

May 15th – May 19th, 2012

Boulder, Colorado, USA
Genes, Brain, and Behavior 2012

14th Annual Meeting of the International Behavioural and Neural Genetics Society

May 15-19

Boulder, CO
USA
Family/Child Care Arrangements:
Contact local host: Marissa.Ehringer@colorado.edu for assistance with finding babysitting services.
Local Organizing Committee
Jerry Stitzel
Marissa Ehringer
Helen Kamens
Todd Darlington
Will Horton
Whitney Melroy
Bridget Carey

Programme Committee
Igor Branchi
Marissa Ehringer
Mary Anne Enoch
Robert Gerlai
Kyung-An Han
Christopher Janus
Jerry Stitzel

Sponsors
National Institute on Alcohol Abuse and Alcoholism (NIAAA)
National Institute of Mental Health (NIMH)
National Institute of Child Health & Human Development (NICHD)
Tuesday, 15th May

8:00 – 20:00  Registration, Sunshine Room

9:30-15:00  Satellite Meeting - Epigenetic Inheritance and the Implications for Complex Traits
            Ballroom

17:30-19:30  Opening Reception
            Courtyard (in case of inclement weather this will be in the Ballroom)
**Wednesday, 16th May**

7:00-9:00  Breakfast buffet  
Foyer outside Ballroom

8:30-9:30  Plenary Speaker  
Ballroom

*Gene-Environment Interplay in Behaviour*  
Marla Sokolowski, University of Toronto, Canada

9:30-10:00  Coffee Break  
Foyer

10:00-12:00  Symposium I  
Ballroom

*Sex, Food, Sleep, Memory Loss*  
Organizer: Josh Dubnau

Looking for sexual selection in the brain: *a behavioral genomics approach to female preference behavior*, Molly Cummings, University of Texas, USA

Fruit flies like a banana: *Graded encoding of food odor value in the Drosophila brain*, Jen Beshal, Cold Spring Harbor Laboratory, USA

Sleeping Together: *Using social interactions to understand the role of sleep in plasticity*, Paul Shaw, Washington University at St. Louis, USA

dCREB2-responsive transcription and long-term memory formation, Jerry Yin, University of Wisconsin, USA

A microRNA-Dopamine receptor genetic module in distinct neural circuits for olfactory arousal and olfactory memory, Josh Dubnau, Cold Spring Harbor Laboratory, USA

12:00-13:30  Lunch break – on your own

13:30-15:30  Selected Talks Session I  
Ballroom

Investigating the long lasting effect of THC exposure during adolescence using a mouse model, Henry Goodfellow, Kings College London, UK

Ethanol-induced courtship disinhibition, Paula Villarreal, University of Texas at El Paso, USA
Interaction between a naturally occurring Chrna4 polymorphism in mice and Chrna5-dependent oral nicotine intake, Jerry Stitzel, University of Colorado at Boulder, USA

Constructing behavior from neurogenomic networks: transcript modules and expression QTLs in the limbic brain, Khyobeni Mozhui, University of Tennessee Health Science Center, USA

Alzheimer’s disease, amyloid beta, and dementia, Christopher Janus, University of Florida, USA

Identification of transposable element RNAs as TDP-43 targets and selective reduction of their binding in frontotemporal lobar degeneration, Wanhe Li, Cold Spring Harbor Laboratory, USA

15:30-16:00 Coffee Break
Foyer

16:00-17:30 IBANGS Executive Committee meeting
Institute for Behavioral Genetics

Thursday, 17th May

7:00-9:00 Breakfast buffet
Foyer outside Ballroom

8:30-9:30 Distinguished Scientist Award Lecture
Ballroom

Genetic and Neural analyses of Dopaminergic Circuits in Habit Learning
Joe Z. Tsien, Georgia Health Sciences University, USA

9:30-10:00 Coffee Break
Foyer

10:00-12:00 Symposium II
Ballroom

Genetic and Epigenetic Effects on Gene Expression and Behavior in Genetically Complex Populations of Monkeys, Mice, and Flies
Organizers: Clarissa Parker and Abraham Palmer

Genetic complexity combined with environmental plasticity at genes important in regulating behavior may favor alternative strategies: Using NGS to identify potential substrates, Mary-Anne Enoch on behalf of Christina Barr, National Institute on Alcohol Abuse and Alcoholism, NIH, USA
Genome-wide association for fear conditioning in an advanced intercross mouse line, Clarissa Parker, University of Chicago, USA

Genetic dissection of genome-wide expression variation in drosophila heads, Stuart Macdonald, University of Kansas, USA

Short-term selective breeding for behavioral traits in heterogeneous stock: Genetic and transcriptional effects, Ovidiu Iancu, Oregon Health & Science University, USA

Allele-specific methylation and genetic association in outbred mice, Leo Schalkwyk, Kings College London, England

12:00-13:30  Lunch Break – on your own

13:30-15:00  Outstanding Travel Awardees
Belle Room

Graduate Student Awardees:
The role of αCaMKII autophosphorylation in the establishment of alcohol addiction. Alanna Easton, King’s College, UK

Novel age-dependent learning deficits in a mouse model of Alzheimer’s disease: implications for translational research. Karienn Montgomery, University of Florida, USA

Post-doctoral Fellow Awardee:
Microsatellite regions upstream of the vole Avpr1a gene contribute to both individual and species differences in receptor expression. Zoe Donaldson, Columbia University, USA.

Junior Faculty Awardee:
Program Note: Stephanie Perreau-Lenz is the outstanding junior faculty travel awardee, but she will be presenting her talk in symposia IV on Friday

15:00-16:00  IBANGS General Business Meeting
Ballroom
-All participants are invited to attend

17:00-19:00  Poster Session
Century Room, 1st floor
Friday, 18th May

7:00-9:00  Breakfast buffet
           Foyer outside Ballroom

8:30-9:30  Plenary Speaker
           Ballroom

NMDA Receptor Blockade and Rapid Behavioral Antidepressant Responses
Lisa M. Monteggia, UT Southwestern Medical Center, USA

9:30-10:00 Coffee Break
            Foyer

10:00-12:00 Symposium III
            Ballroom

Stress, Genes and Environment: Understanding their Interaction in Animal Models of Metabolic and Affective Disorders
Organizers: Chadi Touma and Oliver Ambrée

Effects of early life social experiences on vasopressin- and oxytocin-mediated social and emotional behaviors, Alexa Veenema, Boston College, USA

Social stress, obesity and diabetes: from models to mechanisms, Alessandro Bartolomucci, University of Minnesota, Minneapolis, USA

Genetic predisposition for extremes in stress reactivity: modeling endophenotypes of affective disorders in mice, Chadi Touma, Max Planck Institute of Psychiatry, Germany

S100B in psychiatric disorders: evidence from translational research on gene-environment interactions, Oliver Ambrée, University of Münster, Germany

12:00-13:30 Lunch – on your own

13:30-15:30 Selected Talks Session II
            Ballroom

Adolescent social isolation alters tryptophan hydroxylase 2 mRNA expression in the dorsal raphe nucleus of adult female rats, Jared Kopalman, University of Colorado at Boulder, USA

Genetic and molecular analysis of high anxiety-like behaviors in wild-derived mouse strains, Arika Tanave, The Graduate University for Advanced Studies, Japan
Tissue-specific expression changes in the mouse brain associated with early life stress, Timothy Powell, King's College, UK

An analysis of choroid plexus gene expression in major depressive disorder. Cortney Turner, University of Michigan, USA

Identifying genetic modifiers of the vertebrate stress response system. Karl Clark, Mayo Clinic, USA

What are we really measuring in tests of anxiety in mice? Richard Brown, Dalhousie University, Canada

15:30-16:00 Coffee Break
Foyer

16:00-18:00 Symposium IV
Ballroom

Clock Genes and Drugs of Abuse
Organizer: Alan Rosenwasser

Introductory remarks, Alan M. Rosenwasser, University of Maine, USA

The role of CLOCK in ethanol-related behaviors, Angela Ozburn, University of Pittsburgh, USA

A double whammy: The Per2 mutation leads to additional diurnal phases of ethanol intake and reduced sensitivity to constant-release acamprosate, Allison Brager, Morehouse School of Medicine, USA

The involvement of the clock gene Per2 in mediating stress-induced alcohol drinking behavior in fetal alcohol-exposed mice, Ryan W. Logan, Rutgers University, USA

Per Genes and Addiction, Stephanie Perreau-Lenz, Central Institute of Mental Health, Germany

Discussant, Rainer Spanagel, Central Institute of Mental Health, Germany

19:00-21:30 Social Banquet
Courtyard

Saturday, 19th May

7:00-9:00 Breakfast buffet
Foyer outside Ballroom
8:30-9:15    Remarks about NIAAA funding opportunities by Dr. Matt Reilly
            Ballroom

9:30-11:30   Symposium V
            Ballroom

*Genetic and Neural Influences on Reward Perception*
*Organizers: Christopher Kliethermes & John Crabbe*

*Assessing the role of delta opioid receptors in reinforcement processes: reward
or learning?* Julie Le Merrer, IGBMC, France

*Dysfunction of glutamatergic neurons and altered response to alcohol in the infralimbic
cortex following a history of dependence*, Wolfgang H Sommer, Central Institute of
Mental Health, Germany

*Measuring rewarding effects of drugs in mice and humans*, Dai Stephens, University of
Sussex, UK

*Ethanol reward and aversion in a high drinking selected mouse line*, Amanda Barkley-
Levensen, Oregon Health & Science University, USA

12:00        Meeting adjourned
Gene-environment interplay in behavior

M.B. Sokolowski

I will discuss the relationships between genes, environments and behaviour from both a mechanistic and evolutionary perspective. Examples of gene by environment interactions will be given from the human, rodent and fly literature. A short discussion of epigenetic effects on behaviour and the importance of early experience will also be included. Conservation of gene function in behaviour will be illustrated using the rover/sitter foraging gene that encodes a cGMP dependent protein kinase. Its role in food related behaviours and individual and social learning and memory will be considered. The role of the foraging gene as a modulator of behaviour in worms, flies, beetles and social insects will also be discussed as well as speculations about its role in humans.

1 Department of Ecology and Evolutionary Biology, University of Toronto.

Support: Natural Sciences and Engineering Council of Canada, Canadian Institutes for Health Research, Canadian Institute for Advanced Research.
Looking for sexual selection in the brain: a behavioral genomics approach to female preference behavior

M Cummings¹, M Ramsey¹, R Wong¹,², K Lynch¹

Using genomic profiling techniques with classic model organisms for female mate choice and male coercive mating systems (swordtails and mosquitofish, respectively), we have identified candidate genes as well as candidate neural circuitry for female mate preference behavior. Our swordtail studies have identified genes associated with synaptic plasticity (neuroserpin, neuroligin-3, NMDA-R) that are differentially expressed in mate choice contexts relative to other social environments. Localization studies with swordtails show that neuroserpin expression is elevated in learning and memory centers of the fish brain (Dm, DI) when females exhibit high levels of preference behavior. Comparative studies demonstrate that synaptic plasticity genes exhibit opposing patterns of whole brain gene expression in female brains during male exposure—exhibiting a positive correlation with preference behavior in swordtails (Xiphophorus nigrensis) and a negative relationship in mosquitofish (Gambusia affinis). Mosquitofish females exhibit elevated levels of neuroserpin and neuroligin-3 associated with activity patterns under asocial conditions, yet exhibit downregulation of these genes when females exhibit biases towards males, suggesting that the presence of coercive male mosquitofish may inhibit expression of these genes. Our studies highlight the dynamic and context-dependent genomic response associated with mate choice behavior and begin to identify the critical neural processes shaping sexual selection.

¹ Section of Integrative Biology, University of Texas, Austin, TX 78712
² Department of Biology, North Carolina State University, Raleigh, NC 27695
Fruit flies like a banana: Graded encoding of food odor value in the *Drosophila* brain.

J Beshel¹, Y Zhong¹

Odors are highly evocative, yet how and where in the brain odors derive meaning remains unknown. We first establish Drosophila's partiality for differing food odors, and then show that odor-evoked activity of neurons located outside the canonical olfactory system precisely determines odor value. In vivo two-photon calcium imaging of the fly brain reveals the responsiveness of Drosophila Neuropeptide F (dNPF), the Neuropeptide Y homolog, as much larger to food odors than to non-food odors, including food-odor components. Moreover, hunger similarly elevates neural and behavioral food-odor responses. Remarkably, these neurons are not only necessary, sufficient, and specific to food-odor attraction but the activity amount exactly defines attraction level to, and even preference between, individual food odors. We thus demonstrate the existence of a motivationally-scaled neural 'value signal' accessible from uniquely identifiable cells. Responses are graded within a specific class of stimuli and stable across individuals, making precise predictions about behavior possible.

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Funding Support: Cold Spring Harbor Laboratory and grants from the National Institute of Deafness and Other Communication Disorders (RO1 DC005784) and National Institute of Neurological Disorders and Stroke (RO1 NS064331).
Sleeping Together: Using social interactions to understand the role of sleep in plasticity

Jeffery Donlea, Naren Ramanan and Paul J Shaw

Healthy aging is associated with deficits in cognitive processes, including memory formation, in humans, monkeys, dogs, mice, rats, worms and flies. In the current study, we find that both behavioral and structural plasticity following social enrichment decline with age in Drosophila. We identify dopaminergic signaling as a target for altering plasticity with age; young flies with impaired dopaminergic signaling exhibit deficits in both structural and behavioral plasticity and, conversely, senescence is delayed in aged flies with elevated dopamine levels. Our results also indicate that elevated expression of the transcription factor blistered (bs) in the LNvS delays senescence of plasticity following social enrichment. Together, these data suggest that observing sleep following social enrichment can provide a productive model for identifying mechanisms of plasticity that degrade with age.

Department of Neurobiology, Washington University in St. Louis, 660 S. Euclid Ave, St. Louis, MO.
dCREB2-responsive transcription and long-term memory formation

Anne Tanenhaus¹, Jiabin Zhang¹, Shane Andrews², Jerry C.P. Yin¹,²,³

It is well established that cAMP-responsive signaling, and CREB (dCREB2 in Drosophila)-mediated transcription, is critical for long-term memory formation. Using a new transgenic reporter that allows spatial control of expression, we see that memory formation is correlated with persistent increases in dCREB2 activity which last for a number of days after the end of training. This persistence is inconsistent with the standard view of “immediate early” gene activation and downstream cascades of gene expression. Instead, it suggests that fundamental properties, such as “excitability”, of the neurons in the memory circuit are altered. We are currently testing the functional importance of these persistent changes in transcriptional activity. The kinetics of altered transcriptional activity is also different in various brain regions that are thought to be important for long-term memory formation. Intriguingly, the persistent increases in activity correlate in their timing with the two major times when flies sleep across the day/night cycle, suggesting that sleep-related processes are somehow important.

Recent work on cAMP signaling in cells shows that ligand-receptor-G protein-transmembrane adenylyl cyclase stimulation only alters cAMP in small microdomains underneath the receptor. These changes do not normally “spill over” across the cell. However, there is a second class of adenylyl cyclase molecules that are “soluble” (not transmembrane), and are localized at key subcellular locations around the cell. We are investigating the possibility that this specialized subpool of cAMP may contribute to changes in cell-wide properties, such as “excitability”.

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Funding support: NINDS and NTP training grant
micro-RNA-276a and the Zombie fruit fly

Wanhe Li¹,², Josh Dubnau¹

Olfactory aversive memory in Drosophila involves the convergence of acetylcholinergic CS and dopaminergic US pathways onto mushroom body (MB) neurons. DopR, a type 1 dopamine receptor, is thought to mediate the US inputs onto MB during olfactory learning. But DopR function also is required in the ellipsoid body to mediate arousal to external stimuli. We demonstrate that MicroRNA-276a (miRNAa-276a), like DopR, is required both in MB for memory formation and in ellipsoid body for responses to the CS-odor. miRNAs are ~21–23 nucleotide noncoding RNA transcripts that regulate gene expression at the post-transcriptional level. miRNAs regulate gene expression by binding to complementary sequences in the 3′untranslated regions of target mRNAs. While a growing number of studies demonstrate the importance of micro-RNA function in brain, there still are relatively few examples where individual miRNA genes have been shown to function acutely within specified neural circuits for particular behaviors. We show that miR276a expression is required acutely both in mushroom body and ellipsoid body neurons. In both circuits, the miR appears to target a DA1 type dopamine receptor but this regulatory relationship sub-serves different aspects of olfactory behavior. This miR276a-Dopamine receptor interaction is required in mushroom body neurons to support long-term olfactory memory and in ellipsoid body neurons to modulate olfactory arousal.

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²Graduate Program in Molecular and Cellular Biology, Stony Brook University, Stony Brook, NY 11794, USA.
Investigating the Long Lasting Effect of THC Exposure During Adolescence Using a Mouse Model

Goodfellow H1, Insalata V, 1 Mostert JM1, Murray RM2, Fernandes, C.1

Cannabis is one of the most widely abused recreational drugs and abuse during adolescence has been associated with an increased risk of schizophrenia. When DBA/2J but not C57BL/6J were exposed to delta-9-tetrahydrocannabinol (THC), the principal constituent of cannabis, during adolescence, but not in adulthood, there was a long-lasting effect on social behaviour, a trait altered in schizophrenia. To determine if this long lasting effect on social behaviour was associated with a change in gene expression, microarray analysis was performed on these mice. Genome wide gene expression profiles on the prefrontal cortex of DBA/2J mice exposed to THC or saline during adolescence or adulthood were compared using Affymetrix Exon 1.0 ST microarrays. Pathway analysis of the microarray data using Ingenuity highlighted dopamine receptor signalling as a significantly altered pathway. Also within the top 200 most significantly upregulated genes for the adolescent DBA mice exposed to THC were 3 dopamine receptors types. Altered dopamine signalling is thought to be crucial in the pathology of schizophrenia. Our results from the microarray analysis and the behavioural study support the theory that cannabis exposure during adolescence could lead to an increased vulnerability to schizophrenia by permanently altering the expression of genes within the dopaminergic system.

1 Social, Genetic and Developmental Psychiatry (SGDP) Centre & 2 Department of Psychosis Studies, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF UK

Funding support: Research Councils UK Fellowship. Erasmus scholarship
**Ethanol-induced courtship disinhibition**

P Villarreal\(^1\), GP Aranda\(^1\), J Lim\(^1\), and K-A Han\(^1\)

Behavioral disinhibition such as increased impulsivity and aggression is typically observed in inebriated humans and alcoholics. Moreover, trait behavioral disinhibition has strong correlation with alcohol abuse and addiction, suggesting that disinhibition and addiction have overlapping genetic or neural components. Despite the clinical significance, the neurobiological basis of alcohol-associated behavioral disinhibition is poorly understood. To address this, we employed the powerful genetic model system Drosophila melanogaster. Drosophila males were subjected to ethanol administration once a day for 6 days and their behaviors were recorded and scored. Wild-type males exhibited disinhibited inter-male courtship under the influence of ethanol, and repeated ethanol treatment progressively increased this activity, indicating that the flies developed behavioral sensitization to the ethanol’s effect on disinhibition. The dopamine system is critical for ethanol-induced courtship disinhibition. The synaptic output of dopamine neurons is required for disinhibited courtship while and repeated ethanol treatment decreased tyrosine hydroxylase levels. Genetic manipulation of the dopamine system indicated that D1 receptor activity is crucial for disinhibition and D2 for sensitization. These findings are novel and provide a unique system to unravel the neural and cellular mechanisms underlying ethanol-induced behavioral disinhibition. Supported by the ABMRF/The Foundation for Alcohol Research and NIH/RCMI 5G12RR008124 grants.

\(^1\)Department of Biological Sciences, BBRC Neuroscience and Metabolic Disorders Project, University of Texas at El Paso, TX 79968, USA
Interaction between a naturally occurring *Chrna4* polymorphism in mice and *Chrna5*-dependent oral nicotine intake.

Jerry A. Stitzel\textsuperscript{1,2}, Lauren Ljunghag\textsuperscript{1,2}, Vivian Nguyen\textsuperscript{1} and Susan Kim\textsuperscript{1}

*Chrna4* codes for the nicotinic receptor (nAChR) α4 subunit in mice. A polymorphism has been identified in this gene that results in a threonine to alanine substitution at amino acid 529 of the α4 subunit (T529A). The α4 subunit combines with the β2 subunit and sometimes the α5 subunit to produce α4β2 and α4β2α5 nAChRs. We have demonstrated that the α4 A529 variant affects nAChR function similar to what would be expected if there were an α5 subunit in the nAChR. To test whether the A529 variant of α4 can functionally replace α5 in a measure of the behavioral effects of nicotine, we generated an F2 intercross between C3H/Ibg mice and *Chrna5* KO mice on a C57BL/6 background. C3H/Ibg mice possess the A529 allele and C57BL/6 mice possess the T529 allele of *Chrna4*. The F2 animals were tested for free choice oral nicotine intake, a behavior that we have shown to be affected by *Chrna5* deletion when on a C57BL/6 background. Results indicated that *Chrna5* deletion increased free choice oral nicotine intake in mice homozygous for the T529 allele of *Chrna4*. However, in mice homozygous for the A529 allele, *Chrna5* deletion had no impact on oral nicotine intake. Other known nAChR gene polymorphisms in mice did not alter the affect of *Chrna5* deletion on nicotine intake. These findings support the hypothesis that the A529 variant of α4 acts functionally like α5. The data also demonstrate the potential for natural genetic variants to influence the effects of gene deletions on behavior.

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Supported by DA015663, DA022462, and CA089392
Constructing behavior from neurogenomic networks: transcript modules and expression QTLs in the limbic brain

Khyobeni Mozhui, Lu Lu, Robert W Williams

Networks are a fundamental aspect of complex systems. How an animal behaves and interacts with the environment is defined by information encoded in neural networks. At an even more basic level are networks of molecules (mRNAs, proteins) and genetic variants that drive behavior. In the brain, the transcriptome is organized into modular networks of highly connected transcripts. Can complex emotion-related behavior be more effectively inferred from the summation of such modules than from the discrete effects of component transcripts? To address this, we examine gene expression in two brain regions, the amygdala and hypothalamus. We use inbred mouse strains from the BXD family that have significant genetic divergence in behavioral phenotypes related to the limbic system (e.g., fear response, stress reactivity, anxiety trait). Our analysis shows that transcripts in the amygdala and hypothalamus are clustered into modules that are predictive of function and behavior. The overall network structure is well preserved across brain regions and between the sexes and the high level of preservation indicates a transcriptional system in which mRNAs are organized into stable, functionally cohesive coexpression modules. By incorporating genetic regulatory information to the analysis, we provide a model in which stable transcript networks are regulated by distinct sets of expression QTLs that are both region and sex specific.

Department of Anatomy & Neurobiology, University of Tennessee Health Science Center, Memphis, TN

Supported by the UTHSC Center for Integrative and Translational Genomics, and NIH grants from NIAAA (NIAAA U01AA017590, U01AA13499, U24AA13513, and U01AA014425), and a Human Brain Project from NIDA, NIMH, and NIAAA (P20-DA 21131).
Alzheimer's disease, amyloid beta, and dementia

C. Janus\textsuperscript{1}, P. Chakrabarty\textsuperscript{1}, J. Kim\textsuperscript{2}, T. Golde\textsuperscript{1}

Amyloid precursor protein (\textit{APP}) gene is one of the genetic risk factors implicated in familial forms of Alzheimer's disease (AD). It is now well established that APP transgenic (Tg) mice exhibit cognitive deficits. Amyloid $\beta$ (A$\beta$) is the major component of senile plaques in the brains of AD patients. Lowering A$\beta$ in the brain of TgAPP mice improved their cognitive function. Disappointingly however, the recent series of Phase III clinical trials failed to translate these pre-clinical results into similar positive clinical outcomes.

To identify the role of individual A$\beta$ peptides in dementia, we created TgBRI-A$\beta$ mice that over-express A$\beta$ without APP. The TgBRI-A$\beta$40 mice, over-expressing A$\beta$40, do not develop A$\beta$ deposits even by 24 months of age, while TgBRI-A$\beta$42 mice develop A$\beta$ deposits in the forebrain by 12 months. Both Tg lines showed no apparent abnormalities in locomotor activity and exploratory motivation. Importantly, the TgBRI-A$\beta$ mice showed comparable to control mice spatial memory, associative learning of taste aversion, and context and cued fear conditioned memory at ages of 14 - 16 months coinciding with extensive A$\beta$ deposition in TgBRI-A$\beta$42 mice. Also, the levels of A$\beta$40 and A$\beta$42 species were not correlated with the variability in memory scores, suggesting dissociation between the A$\beta$ and dementia. Concluding, the sole over-expression of A$\beta$ did not induce AD-like dementia and its underlying A$\beta$ pathology in a mouse model, which suggests that the investigation of the mechanism of dementia targeting selectively A$\beta$ may be less useful with respect to development of novel therapies for AD.

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\textsuperscript{2} Dept. of Neurology, Washington University School of Medicine, 660 S. Euclid Box 8111, St. Louis, MO 63110
Identification of transposable element RNAs as TDP-43 targets and selective reduction of their binding in frontotemporal lobar degeneration

W Li1, 2, L Prazak1, Y Jin1, M Hammell1, and J Dubnau1

Mutations in a multifunctional RNA binding protein called TDP-43 cause many familial and some sporadic cases of amyotrophic lateral sclerosis (ALS). Accumulation of TDP-43 containing cytoplasmic inclusions is a shared pathological hallmark in a broad spectrum of neurodegenerative disorders, including ALS, frontotemporal lobar degeneration (FTLD) and Alzheimer’s disease. Despite considerable progress, the mechanisms that link TDP-43 to neurodegeneration still are unclear. Transposable elements (TEs) are highly abundant mobile genetic elements that constitute a large fraction of most eukaryotic genomes. Recent studies showed that TEs can be active during brain development and unregulated specific TE expression occurs in several neurodegenerative disorders. Because elevated expression of a human ERV (endogenous retroviruses, a subfamily of TEs) has been detected in cerebral-spinal fluid of patients with ALS, we investigated whether the RNA targets of TDP-43 targets include transposon-derived transcripts. By mining sequencing datasets, we uncovered extensive association between TE transcripts and TDP-43. Strikingly, this TDP-43-TEs association is reduced in brain tissues from FTLD patients, consistent with the emerging hypothesis that TE misregulation contributes to the pathology of neurodegenerative disorders.

1. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA.
2. Graduate Program in Molecular and Cellular Biology, Stony Brook University, Stony Brook, NY 11794, USA.

Funding Support: NIH TR01 5R01NS067690-03 and Dart Neuroscience LLC
Genetic and Neural analyses of Dopaminergic Circuits in Habit Learning

Joe Z. Tsien

Decoding the upstream pathways regulating dopamine is crucial for understanding habit learning, an important cognitive function that depends on the striatum. Activities of midbrain dopaminergic neurons are regulated by cortical and subcortical signals among which glutamatergic afferents provide excitatory inputs. Cognitive implications of glutamatergic afferents in regulating and engaging dopamine signals during habit learning however remain unclear. Our recent studies show that mice with dopaminergic neuron-specific NMDAR1 deletion are impaired in a variety of habit learning tasks but are normal in some other dopamine modulated functions such as locomotor activities, goal directed learning, and spatial reference memories. In vivo recording revealed that in the mutant mice, a reward predicting cue can still induce albeit greatly attenuated bursting activities in the DA neurons. Our results suggest that NMDA receptor-mediated integration of glutamatergic inputs at DA neurons serve as a crucial cellular hub for habit learning. I will also present some new data on the neural correlates of habit in the neural circuits regulated by dopamine.

Brain and Behavior Discovery Institute and Department of Neurology, Georgia Health Sciences University, Augusta, GA 30912, USA
Genetic Complexity Combined with Environmental Plasticity at Genes Important in Regulating Behavior May Favor Alternative Strategies- Using NGS to Identify Potential Substrates

Yuan, Q, Zhou Z, Lindell SG, Higley JD, Suomi SJ, Schwandt ML, Baker M, Goldman D, Barr CS

Background: Adaptations to unpredictable or stressful environmental conditions can occur at both the species and the individual levels. Searching for genes at which there is both increased genetic diversity and stress-mediated epigenetic regulation may be a particularly powerful approach for identifying genes that play critical roles in adaptation and survival. Methods: Brains (N=14) were archived from individuals in an outbred population of rhesus macaques that were reared in the presence or absence of stress. Chromatin Immunoprecipitation was performed with an antibody against H3K4me3. ChIP-Sequencing was performed on a on a SolexaG2A sequencer. Comparative genome analysis was performed using the bioinformatics information available through the UCSC Gateway. Effects of stress exposure on levels H3K4me3 binding were determined using ANOVA. Results: Using a parallel next-gen sequencing, we sequenced the whole mRNA transcriptome and H3K4me3-marked (histone H3 trimethylated at lysine 4) DNA regions in hippocampus from rhesus macaques. At least one SNP was identified in >16,000 annotated macaque genes. Accuracy of macaque SNP identification was conservatively estimated to be >90%. Among the genes at which there was both stress-related epigenetic regulation (difference in H3K4me3 binding) and increased SNP density were the SLC6A4 (serotonin transporter) and OXTR (Oxytocin receptor) genes, both of which have polymorphisms that have been linked to stress-related problems. Genotype-phenotype correlations will be presented that support a role for polymorphisms in moderating environmental sensitivity and response. Conclusions: There were a number of genes at which we observed increased diversity and epigenetic regulation, thus potentially favoring alternative strategies. Varied responses to stressful conditions among individuals within a group or species may confer a selective advantage in some contexts, yet increased vulnerability to stress-related disorders in modern humans.

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD
Genome-wide association for fear conditioning in an advanced intercross mouse line

Clarissa C. Parker¹, Greta Sokoloff¹, Riyan Cheng¹, Abraham A. Palmer¹,²

Populations with greater numbers of accumulated recombinations such as advanced intercross lines (AILs) allow for more precise mapping due to a breakdown in linkage disequilibrium. Because AILs are derived from two inbred founders, they maintain the simplicity of more traditional crosses while allowing GWAS to be performed in a situation where all alleles are common and where every marker that differs between the parental strains is perfectly informative. We used a C57BL/6J x DBA/2J F₂ intercross (n = 620) and a C57BL/6J x DBA/2J F₈ AIL (n = 567) to fine-map quantitative trait loci (QTL) associated with fear conditioning (FC). We conducted an integrated genome-wide association analysis in QTLRel and identified five highly significant QTL affecting freezing to context as well as four highly significant QTL associated with freezing to cue. The average percent decrease in QTL width between the F₂ and the integrated analysis was 59.2%. Next, we exploited bioinformatic sequence and expression data to identify candidate genes based on the existence of non-synonymous coding polymorphisms and/or expression QTLs in amygdala, hippocampus, and whole brain. We identified multiple candidate genes may be relevant to fear learning in animal models (Bcl2, Btg2, Dbi, Gabr1b, Lypd1, Pam and Rgs14) or PTSD in humans (Gabra2, Oprm1 and Trkb). The integration of F₂ and AIL data in conjunction with sequence and gene expression data maintains the advantages of studying FC in model organisms while significantly improving resolution over previous approaches.

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Genetic Dissection of Genomewide Expression Variation in *Drosophila* Heads

SJ Macdonald ¹, BJ Sanderson ¹

*Drosophila* is widely employed as a genetic system to understand fundamental aspects of neurogenesis and behavior, and is increasingly recognized as an important model for the study of human neurodegenerative disease and the action of drugs of abuse. As with all complex, polygenic traits identifying the molecular pathways and causative genes responsible for variation in these phenotypes is challenging. Given the community interest in genetically dissecting neurobehavioral traits in flies, we took advantage of a novel resource for genetic analysis to characterize quantitative variation in transcript abundance specifically in *Drosophila* heads. The *Drosophila* Synthetic Population Resource (DPSR) is composed of over 1,600 genotyped Recombinant Inbred Lines (RILs) derived from highly-recombinant synthetic laboratory populations. These populations were initially founded by multiple inbred strains, ensuring high functional allelic diversity in the DSPR. We generated 600 heterozygous genotypes - the progeny of intercrosses between DSPR lines - isolated RNA from adult female heads, and subjected each sample to microarray analysis. These data allow us to construct gene networks and capture the full biological complexity of the pathways involved in gene regulation in the *Drosophila* head and brain. Genomewide expression QTL (eQTL) analysis also provides a high-resolution picture of the location, effect, and population frequency of loci that influence expression variation in the head. In addition, researchers using the DSPR to genetically dissect neuronal or behavioral phenotypes will be able to exploit our eQTL data for a systems-level analysis of trait variation, and quickly home in on likely candidate genes.

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Short-term Selective Breeding for Behavioral Traits in Heterogeneous Stock: Genetic and Transcriptional Effects

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We performed short term bi-directional selective breeding for haloperidol-induced catalepsy, starting from three mouse populations of increasingly complex genetic structure: an F\textsubscript{2} intercross, a heterogeneous stock formed by crossing four inbred strains (HS4), and a heterogeneous stock (HS-CC) formed by crossing the eight strains found in the collaborative cross. All three selections were successful, with large differences in haloperidol response emerging within three generations. Next, we examined the genetic differences emerging between the selected lines; we also compared them with the starting populations. Using an imputation algorithm and genotyping data, we estimated the most likely haplotype structure of each individual sample. This procedure revealed significant allele fixation in each of the selected lines as compared with the starting populations. Gene expression data were obtained from the striatum using the Illumina WG 8.2 array. Surprisingly, in spite of large phenotypic differences, absolute level gene expression changes were modest. In contrast, the gene coexpression patterns changed significantly, as revealed by analysis using the weighted gene co-expression network analysis (WGCNA). In particular, we detected three modules (groups of coexpressed genes) that 1) are richly annotated with neurobehavioral traits, and 2) show coexpression changes that are detectable independently across all three genetic backgrounds.

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Allele-specific methylation and genetic association in outbred mice

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We have been using the Boulder heterogeneous mouse stock, founded in the early 1970s and derived from an eight-way cross of A, AKR, BALB/c, C3H, C57BL/6, DBA/2, Is and RIII inbred mouse strains. We have successfully used this stock to examine associations between specific candidate genes and behavior, and now we are working on improving genetic association analysis by adding gene expression and allele-specific DNA methylation to the model. Our study of allele-specific DNA methylation (ASM) in human showed this phenomenon to be widespread, with an estimated 35000 genomic sites. We have extended the assay to mouse using the mouse diversity array, where there are 54558 potentially informative sites for the HS population. This is a smaller number than in our human study because a large number of the SNPs on the mouse array are not polymorphic among the classical strains. Nevertheless the data look encouraging. Of the known imprinting DMRs, three overlap with informative sites in our assay (all at the Nnat locus) and these show clear non-cis ASM, and we see clear evidence of ASM at about 3% of informative sites (compared to 1.5% in our human study).

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The role of αCaMKII autophosphorylation in the establishment of alcohol addiction

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The development of addiction is thought to involve learning and memory processes. Ca2+/calmodulin dependent protein kinase II (CaMKII) is important for learning and memory formation. Alpha CaMKII can switch to an autonomous mode of activity upon autophosphorylation, allowing signals to be potentiated for longer within the cell, thereby accelerating learning. There is a growing body of research supporting a role for αCaMKII in addictive pathways, we therefore investigated whether autophosphorylation plays a role in the motivational and rewarding effects of alcohol. We used αCaMKII autophosphorylation deficient T286A (Mt), heterozygous (Ht) and wild type (WT) mice to examine alcohol drinking behaviour, monoaminergic activity in the NAcc and the PFC after acute and subchronic alcohol exposure, alcohol bioavailability and alcohol-induced conditioned place preference. We found that alcohol drinking was established at a slower rate in αCaMKII Mt mice compared to WT animals. An effect which can be attributed to the absence of an alcohol induced-dopamine increase in the NAcc of Mt mice. There was no genotypic difference in alcohol bioavailability and the loss of the righting reflex. Alcohol-induced CPP was established faster in αCaMKII Mt mice. Together with an enhanced serotonergic response this suggests a role for αCaMKII autophosphorylation predominantly in the negative reinforcing effects of alcohol. The present data indicate a complex role for αCaMKII in the motivational and reinforcing effects of alcohol, and suggests that αCaMKII autophosphorylation controls the speed at which alcohol-addiction related behaviours are established.

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One hindrance to the development of interventions for Alzheimer's disease (AD) is the absence of assays that identify individuals at early preclinical stages ideal for intervention, and that translate well between rodent models and humans. Thus, there is interest in translational non-verbal tasks that are sensitive to mild decrements in vulnerable brain circuitry. The goal of the current study was to develop a mouse analog of human transfer learning and to determine if it was sensitive to pathological changes in mouse models of AD. The task involves a series of concurrent discriminations that contain 2 features (odor and digging medium) and then requires transferring the learned information into new configurations in which the irrelevant feature is altered (transfer learning). Initial lesion studies determined that transfer learning is hippocampal-dependent. Subsequent studies in 2 transgenic mouse models that have AD-like pathology (APPswePSEN1dE9)85Dbo/o and APPSwDI/mNOS2–/–) showed robust age-dependent deficits in transfer learning, and this impairment occurs earlier than did those assessed by the Morris water maze (in APP/PS1). An additional feature of the task is that it is resistant to previous experiences, making it ideal for within-subject design experiments. Current experiments are directed at determining which molecular changes, particularly at the synaptic level, may be related to onset and severity of transfer learning deficits. These data support that transfer learning is a sensitive, robust hippocampal-dependent assay for mouse models of AD, and indicate that this task should be a useful tool for assessment of therapeutic interventions.

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Microsatellite regions upstream of the vole Avpr1a gene contribute to both individual and species differences in receptor expression

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Polygamous meadow voles and monogamous prairie voles demonstrate striking differences in social behavior that are mediated, at least in part, by differences in neural expression of the vasopressin V1a receptor (V1aR). In addition, prairie voles also display individual variation in V1aR expression, which has been implicated in behavioral variation within this species. In order to explore the genetic mechanisms contributing to these differences in vivo, we focused on dissecting the role of the proximal 5' flanking region and highly variable microsatellite element in the vole vasopressin receptor 1a gene (Avpr1a), a region that has been linked to variation in expression patterns and behavior. To achieve this goal, we created three lines of knock-in mice. In all three, 3.5 kb of the mouse Avpr1a 5'flanking region was replaced by prairie vole sequence, but each line differed only with regard to the microsatellite element – either from meadow vole or the prairie vole long or prairie vole short variants. Using these mouse lines, we found that both species differences and intra-species variation in microsatellite structure contribute to variation in gene expression. The mice with the prairie vole microsatellite had higher levels of V1aR in the thalamus, central amygdala, and dentate gyrus, compared to the mice with the meadow vole microsatellite. Furthermore, comparison of mouse lines with long and short versions of the prairie microsatellite revealed differences in levels of V1aR in the dentate gyrus. This work provides direct evidence that variation in the vole Avpr1a microsatellite modulates V1aR patterns within the brain, potentially providing an evolutionary mechanism underlying V1a-dependent behavioral diversity both within and between these species.

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NMDA Receptor Blockade and Rapid Behavioral Antidepressant Responses

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Clinical studies consistently demonstrate that a single sub-psychomimetic dose of ketamine, an ionotropic glutamatergic n-methyl-d-aspartate receptor (NMDAR) antagonist, produces fast-acting antidepressant responses in patients suffering from major depressive disorder (MDD), although the underlying mechanism is unclear. Depressed patients report alleviation of MDD symptoms within two hours of a single low-dose intravenous infusion of ketamine with effects lasting up to two weeks, unlike traditional antidepressants (i.e. serotonin reuptake inhibitors), which take weeks to reach efficacy. This delay is a major drawback to current MDD therapies, leaving a need for faster acting antidepressants particularly for suicide-risk patients. Ketamine’s ability to produce rapidly acting, long-lasting antidepressant responses in depressed patients provides a unique opportunity to investigate underlying cellular mechanisms. Using a variety of behavioral techniques we examined the ability of ketamine, and other NMDAR antagonists, to trigger a rapid antidepressant response. We find that ketamine, as well as other NMDA receptor antagonists, produce fast-acting behavioral antidepressant-like effects in mouse models that are dependent on rapid synthesis of BDNF. Furthermore, we find that mice lacking BDNF or trkB receptors that mediate BDNF signalling do not respond to ketamine treatment. Our findings suggest that BDNF synthesis regulation by NMDA receptors may serve as a viable therapeutic target for fast-acting antidepressant development.

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Effects of early life social experiences on vasopressin- and oxytocin-mediated social and emotional behaviors

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The early life social environment has profound effects on brain development and subsequent expression of social and emotional behaviors. Vasopressin and oxytocin are expressed in the brain during early development and are important regulators of social behavior. This suggests that early life social experiences may alter social behaviors via changes in the vasopressin and/or oxytocin systems. To test this hypothesis, and to gain mechanistic insights, we have utilized two rodent models mimicking either a deprived early social environment (maternal separation) or an adverse early social environment (peer victimization). Maternal separation (rat or mouse litters separated from the dam for 3 h per day during the first two weeks of life) was found to increase aggressive behaviors during juvenile play-fighting and adult aggression. These behavioral alterations were associated with alterations in oxytocin and vasopressin systems in the brain. We also found a causal relationship between changes in vasopressin responsiveness in the lateral septum and impaired social recognition in maternally separated rats. Peer victimization (a 3-week-old male rat, the “victim”, housed with two older same-sex rats for a period of two weeks) was found to decrease dominant behaviors and increase social investigation during juvenile play-fighting. Peer victimization also increased anxiety-related behavior. We are currently investigating changes in vasopressin and oxytocin systems in this model. These initial findings suggest that differences in the quality of the early life social environment result in the differential expression of social and emotional behaviors, likely mediated, in part, via changes in vasopressin and oxytocin brain systems.

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Social stress, obesity and diabetes: from models to mechanisms

A Bartolomucci

Epidemiological evidence demonstrates that psychiatric and metabolic diseases are rising exponentially to pandemic level. A substantial number of obese individuals show eating disorders, psychiatric conditions, stressful life events, more medical complaints and poorer quality of life. This parallel increase in incidence of seemingly independent diseases has long been suspected to be due to common underlying causal factors including genetic predisposition and exposure to adverse environment. Gene-Environment interaction has been postulated to play a major role to explain this alarming rise in stress-related disease. Unfortunately, current animal models largely fail to recapitulate the vast array of symptoms which are observed in the obese human population. We developed a naturalistic mouse model of chronic subordination stress (CSS) and propose this as an equivalent to the stress-obesity syndrome. CSS mice develop a syndrome characterized by hypothalamus-pituitary-adrenocortical axis dysfunction, depression-like behaviors as well as autonomic and immune-endocrine changes. A robust phenotype in CSS mice is the development of hyperphagia and vulnerability to obesity, metabolic-like and type-2 diabetes-like syndromes. To understand the molecular basis of individual vulnerability and gene-environment interaction we compared the metabolic and behavioral consequences of CSS in different inbred strains of mice differing in metabolic vulnerability to stress (CD-1, C57BL6/J and 129SvEV) and transgenic animal models (5-HTT, VGF, NP1Y1Rfloxed). Results will be discussed in a comprehensive pathophysiological perspective to stress-related disease vulnerability. In conclusion, our highly innovative mouse model of CSS represents a uniquely valuable opportunity to identify the underlying molecular mechanisms and generate testable predictions for innovative therapies.

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Genetic predisposition for extremes in stress reactivity: modeling endophenotypes of affective disorders in mice

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Alterations of the stress hormone system, particularly dysregulation of the HPA axis, play a prominent role in the pathophysiology of major depression. We therefore generated a new animal model comprising the neuroendocrine core symptoms of increased or decreased stress reactivity. Utilizing a selective breeding approach, three independent mouse lines were established from an outbred population of CD-1 mice according to the outcome of a ‘stress reactivity test’ (SRT). Mice showing a very high, an intermediate or a very low secretion of corticosterone in the SRT were selected for the ‘high reactivity’ (HR), ‘intermediate reactivity’ (IR), and the ‘low reactivity’ (LR) breeding line, respectively. Already in the first generation, significant differences in HPA axis reactivity between HR, IR and LR mice were observed. These differences remained stable across all subsequent generations and could be increased by selective inbreeding, indicating a genetically linked trait. In addition to pronounced differences in neuroendocrine functions, extensive characterization of the three mouse lines revealed effects on emotional behaviors, cognitive functions, sleep measures, neurophysiological parameters and molecular markers, pointing to further similarities with depressed patients, particularly when the subtypes of melancholic and atypical depression are considered. Our results indicate that distinct mechanisms influencing the function and regulation of the HPA axis seem to mediate the respective behavioral and neurobiological endophenotypes. Thus, the generated HR/IR/LR mouse lines are a promising model to elucidate the molecular pathways and genetic underpinnings of altered stress reactivity, including gene-environment interactions crucially involved in bringing about the pathological phenotype seen in affective disorders.

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S100B in psychiatric disorders: evidence from translational research

Oliver Ambrée

Genetic variants encoding for the Ca\textsuperscript{2+}-binding protein S100B, which is mainly produced in astrocytes, are associated with psychiatric disorders. These “risk variants” correlate with higher S100B expression in serum and post-mortem frontal cortex mRNA. Also in patients suffering from depression elevated serum levels of S100B were found, however correlating with an improved treatment response. So far it is not clear whether elevated S100B levels contribute to the development of psychiatric symptoms or if they are a consequence of pathophysiological states mediating protective or compensatory effects as neurotrophic factor. A recent study in our lab investigated the effects of elevated S100B levels in overexpressing transgenic mice and psychosocial stress on emotional behavior. After wild type and S100B transgenic mice were either housed under stable or unstable social conditions during adolescence we analyzed their behavior in the open-field, dark-light and novelty-induced suppression of feeding tests. All animals from unstable social conditions independently of their genotype showed less locomotion during the first minute in a novel environment. When raised in stable social conditions S100B overexpressing mice showed less anxiety-like behavior than wild types. When they grew up under unstable social conditions however, they were more anxious and did not differ from wild types. These results of a gene-environment interaction suggest that S100B overexpression leads to a more plastic phenotype, which is rather advantageous in a stress-free and secure environment, while it is disadvantageous if the environment is too stressful. Therefore so-called “risk variants” in evolutionary terms might rather be called “plastic variants”.

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Adolescent social isolation alters tryptophan hydroxylase 2 mRNA expression in the dorsal raphe nucleus of adult female rats.

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Adverse early life experience is thought to increase an individual’s susceptibility to mental health disorders, including anxiety disorders and depression, later in life. Our previous studies have shown that post-weaning social isolation of female rats during a critical period of development sensitizes an anxiety-related serotonergic dorsal raphe nucleus (DR)-basolateral amygdala circuit in adulthood. Therefore, we investigated the effects of post-weaning social isolation of female rats on anxiety-like behavior in a social interaction test. In addition, we also examined how post-weaning social isolation, in combination with a challenge with the anxiogenic drug, N-methyl-beta-carboline-3-carboxamide (FG-7142; a partial inverse agonist at the benzodiazepine allosteric site on the GABAₐ receptor), affects anxiety-like behavior in the home cage and tryptophan hydroxylase 2 mRNA (tph2) expression in the DR of female rats using in situ hybridization. Juvenile female rats were reared in isolation or groups of three for a 3-week period from weaning (postnatal day (P) 21 to mid-adolescence (P42)), after which all rats were group-reared for an additional 2 weeks until adulthood. Among vehicle-treated rats, isolation-reared rats had decreased tph2 mRNA expression in subdivisions of the DR. Isolation-reared rats, but not group-reared rats, responded to FG-7142 with increased duration of vigilance and arousal behaviors. In addition, FG-7142 decreased tph2 expression in the entire DR of group-reared rats but had no effect in isolation-reared rats. These data suggest that adolescent social isolation alters the effects of stress-related stimuli on behavior and serotonergic systems, which have been implicated in the pathophysiology of stress-related neuropsychiatric disorders.

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Genetic and Molecular Analysis of High Anxiety-like Behaviors in Wild-derived Mouse Strain

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Wild-derived mouse strain MSM/Ms (MSM) still shows wildness behaviors which had been lost in laboratory mice during domestication and inbreeding. A subset of these wildness behaviors is associated with high anxiety-like behaviors. We previously conducted genetic mapping of anxiety-like behaviors, using consomic strains. Each consomic strain has one pair of chromosomes of MSM which has been replaced by the corresponding chromosome on C57BL/6 (B6) genetic background. We found that a consomic strain, which carries MSM-derived Chr17, shows high anxiety-like behaviors. In this study, 1) we conducted a fine mapping of high anxiety-like behaviors, 2) and analyzed a candidate gene. 1) We established a series of sub-consomic strains, which carry partial segment of MSM-derived Chr17. In the results of genetic analyses of open-field behaviors using the sub-consomic strains, we successfully mapped a genetic locus into about 2Mb region at the distal end of Chr17, in which two protein coding genes, \textit{Adcyap1} and \textit{Mettl4}, are located. 2) The product of \textit{Adcyap1} gene is known as the neuropeptide, PACAP, which increases the stress responses. Although there was no non-synonymous mutation in \textit{Adcyap1} gene between MSM and B6, qRT-PCR analysis showed that the mRNA levels of \textit{Adcyap1} gene were significantly higher in the sub-consomic strains. In addition, the ratio of splice variants of \textit{Adcyap1} gene was clearly different between classical laboratory strains and wild-derived strains. We think that this altered mRNA level of \textit{Adcyap1} gene leads to higher level of PACAP and is related to the increased anxiety-like behaviors in wild-derived strains.

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Tissue-specific expression changes in the mouse brain associated with early life stress

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**Background:** Research suggests that early stressful life events can induce gene expression changes that subsequently increase the chances of developing psychiatric illness in adulthood. The current study aimed to investigate the effects of early life stress on genome-wide expression in two key areas of the brain involved in stress and depression, the hypothalamus and hippocampus. Furthermore, we aimed to consider whether different genetic backgrounds (G) in the presence of the same early life stress (E) resulted in differential gene expression (GxE) in the two key brain regions. **Methods:** A maternal separation paradigm in two inbred strains of mice, C57BL/6J and DBA/2J, was used to model early life stress in humans. Mice were assigned to either a control (n=10 C57BL/6J, n=13 DBA/2J) or separated group (n=9 C57BL/6J, n=10 DBA/2J). Separated groups underwent maternal separation at postnatal day 9 for 24 hours, and separated and controls underwent culling at week 15. The hippocampus and hypothalamus were dissected and RNA was extracted. cDNA was synthesized *in vitro* for use on Affymetrix Mouse Gene Chip microarrays. **Results:** There were six gene expression changes considered to be true discoveries under the False Discovery Rate (q<0.2). Three gene expression changes were found in the hippocampus (*Wnt4, Rasgrf1, Atp6v0b*), one expression change in the hypothalamus (*Tmem208*), and two expression changes across both tissues (*Insig1, Rbm3*). Results did not reveal any GxEs. **Conclusions:** Gene expression hits have functional relevance not only to depression by a variety of other illnesses.

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An analysis of choroid plexus gene expression in major depressive disorder

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The choroid plexus (CP) functions to produce cerebrospinal fluid, remove byproducts, and provide structural support for the brain. The CP also affects nervous system function by playing a role in neuroendocrine signaling. However, its characterization in the human post-mortem brain, as well as the role that this structure may play in Major Depressive Disorder (MDD) is relatively unknown. To investigate which of the many functions of the choroid plexus may be altered in MDD, we analyzed the post-mortem choroid plexus of six controls (5 males and 1 female) and six individuals with MDD (4 males and 2 females). We performed laser capture microscopy of the choroid plexus at the level of the dentate gyrus. Next, we extracted, amplified, labeled and hybridized the cRNA to Illumina BeadChips to assess gene expression. We also analyzed the results using Ingenuity Pathway Analysis. In controls, the most highly abundant transcript was transthyretin. There were also six ribosomal proteins among the 14 most abundantly expressed transcripts. Using BeadStudio software, we identified 169 transcripts differentially expressed between controls and MDD. There were 43 transcripts upregulated and 126 transcripts downregulated in MDD. Using pathway analysis (Ingenuity) to examine these altered mRNAs, we noted that the top network included multiple members of the extracellular matrix. These results suggest that a large amount of protein synthesis may naturally occur in the choroid plexus. Finally, the extracellular matrix of the choroid plexus may be altered in MDD, suggesting an altered blood-CSF-brain barrier.

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Identifying genetic modifiers of the vertebrate stress response system


The vertebrate stress response system (SRS) is a diverse suite of neuronal, endocrine, and behavioral response mechanisms that plays a key role in environmental interactions. The clinical significance of stress-aggravated disorders is extremely high. Heritable genetic factors and interaction with the environment modify SRS function and responses to stressors. The identity of the genetic factors that modify or influence SRS are mostly unknown since much of the vertebrate SRS is not conserved in traditional genetic models like yeast, Drosophila, or C. elegans. Therefore, our lab is screening a panel of revertible, expression-tagged insertional zebrafish (Danio rerio) mutants being produced at the Mayo Clinic to find genetic modifiers of the vertebrate SRS. These dominantly-marked mutant alleles permit rapid screening of single gene contributions to quantitative biological traits, including behavioral genetics. We are screening selected mutant lines and have identified six lines with an altered response to hyperosmotic stress, including pbx1 and atp1b2a mutants. To aid in further investigation of these mutants, we have produced transgenic fish (SR4G) that produce a short half-life (4-hour) GFP when glucocorticoid receptor activates transcription in response to cortisol. We are examining these mutant lines for altered responses to other (non-salt) stressors and/or altered glucocorticoid receptor activation levels using SR4G fish. Identifying genetic modifiers of the SRS could aid in susceptibility testing or treatment of stress-aggravated disorders.

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What are we really measuring in tests of anxiety in mice?

RE Brown, RK Gunn, TP O’Leary

Anxiety in mice is measured in the elevated plus maze (EPM; Hogg, 1996, Pharm Biochem Behav, 54, 21-30); open field (OF; Prut & Belzung, 2003, Eur J Pharm, 463, 3-33); and light/dark box (LDB; Bourin & Hascoet, 2003, Eur J Pharm, 463, 55-65), and studies often use all three (Kliethermes et al., 2005, Neurosci Biobehav Rev, 28, 837-50). We examined anxiety and locomotor behavior in 10 week old male and female mice of 15 inbred strains (129S1/SvImJ, A/J, AKR/J, BALB/cByJ, BALB/cJ, BTBR T+ tf/tf, C3H/HeJ, C57BL/6J, CAST/EiJ, DBA/2J, FVB/NJ, MOLF/EiJ, SJL/J, SM/J and SPRET/EiJ) on the EPM, LDB and OF. Across all three tests we found that (1) measures of locomotion are significantly positively correlated; (2) frequency of defecations are highly positively correlated; (3) behavioral measures of anxiety are poorly correlated, and; (4) within each test, measures of anxiety and locomotion are correlated. In a factor analysis locomotor measures accounted for 22.2% of the variance, whereas anxiety-related measures accounted for only a small proportion of the variance. This analysis casts doubt on the concept of genetically determined strain differences in a “trait” of anxiety and indicates that locomotor behaviors are the most reliable measures of strain and sex differences in these apparatus. This suggests that we must reconsider the concept of strain-specific “anxiety” traits and focus on activity levels. Whether or not newly designed apparatus for measuring anxiety such as the triple-test (Fraser et al., Psychopharm, 2010, 211, 99-112) will help us resolve this issue is being examined.

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The Role of CLOCK in Ethanol-Related Behaviors

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Our lab has identified a role for the circadian gene, Clock, in the regulation of drug reward. Mice bearing a dominant negative mutation in the Clock gene (ClockΔ19 mice) exhibit increased cocaine sensitivity and preference. These mice also exhibit reduced anxiety- and depression-like behavior, increased intracranial self-stimulation, and increased dopaminergic activity in the ventral tegmental area (VTA). To further understand the role of Clock in drug reward, we assessed the role of Clock in ethanol-related behaviors.

We measured ethanol intake (two-bottle choice paradigm), conditioned place preference (CPP; 2 g/kg dose), conditioned taste aversion (CTA; 2 g/kg dose), acute functional tolerance (AFT; two injections of 2 g/kg dose separated by rotarod recovery and BEC measurements), and clearance (BEC levels after a 4 g/kg dose) in ClockΔ19 mutants and their WT counterparts. To determine if Clock expression in the VTA is important for modulating ethanol intake, we stereotaxically injected AAV-Clock-shRNA or AAV-Scramble-shRNA and measured ethanol intake (two-bottle choice paradigm).

ClockΔ19 mice exhibited increased ethanol intake (preference p<0.05; consumption p<0.05). ClockΔ19 and WT mice developed ethanol-induced CPP, CTA, and AFT to a similar extent and exhibited no differences in ethanol clearance. Preliminary results indicate a strong trend for increased ethanol preference and consumption in mice that were injected with AAV-Clock-shRNA as compared to AAV-Scramble-shRNA (preference p=0.07; consumption p=0.1). We have identified a significant role for Clock in the VTA as a negative regulator of ethanol intake using mutant mice and RNA interference.

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A DOUBLE WHAMMY: THE \textit{PER2} MUTATION LEADS TO ADDITIONAL DIURNAL PHASES OF ETHANOL INTAKE AND REDUCED SENSITIVITY TO CONSTANT-RELEASE ACAMPROSATE

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The neurochemical bases for elevated ethanol intake and preference in \textit{PER2}-mutant mice and subsequent suppression by acamprosate are widely known. However, little is known where in the brain acamprosate acts to suppress ethanol intake and preference or how the alteration of circadian timing manifest from \textit{PER2} mutation complements elevated ethanol intake and preference in \textit{PER2}-mutants. To approach this, we compared diurnal rhythms and overall levels of ethanol intake, preference, and systemic concentrations in wild-type (WT) and \textit{PER2}-mutant mice prior to and during short-term systemic administration of acamprosate or long-term constant-release of acamprosate from reward and circadian brain areas. Actographic and microdialysis measurements revealed that \textit{PER2}-mutants had additional circadian phases and overall higher levels of ethanol intake, preference, and systemic concentrations compared with WTs that were concurrent with a 2 hr phase-advance in and subsequent extension of wakefulness. Systemic acamprosate reduced the number of ethanol drinking episodes and overall levels of ethanol intake, preference, and systemic concentrations at each circadian phase, but did not alter the general diurnal pattern of ethanol intake in both strains. Constant-release of acamprosate (or blank) over 30 days from micropellets in specific reward (nucleus accumbens, ventral and peduculopontine tegmental areas), circadian (suprachiasmatic nucleus and intergeniculate leaflet), and control (hippocampus) regions effectively mapped brain area sensitivities to acamprosate and revealed reduced suppression of ethanol intake and preference over shorter days in \textit{PER2}-mutants compared with WTs. Moreover, these data offer circadian and neurobiological support for \textit{PER2} modulation of ethanol intake and sensitivity to acamprosate treatment.

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The involvement of the clock gene Per2 in mediating stress-induced alcohol drinking behavior in fetal alcohol-exposed mice

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Both circadian and stress-response systems are fundamental mechanisms for adapting to environmental change, however little is known about the integration of these systems and how they may influence alcohol use. In humans and animals, excessive alcohol use can lead to circadian disruption with altered expression of clock genes, in particular the Period genes (\textit{Per1,2}), which may be associated with changes in diurnal rhythms of the hypothalamic pituitary adrenal (HPA) axis. Moreover, alterations in circadian rhythms of corticosterone and proopiomelanocortin (\textit{POMC}) genes, two key regulators of the stress system, are observed in \textit{Per2} mutant mice. Interestingly, \textit{Per2} seems to be involved in the alcohol induced stimulatory response of POMC neurons, further providing a connection between clock genes, stress regulation, and alcohol. Therefore, we sought to further explore the involvement of \textit{Per2} in stress-related alcohol drinking behavior, and the possible association to alcohol exposure during early development. In response to an acute stressor, alcohol exposed C57BL6 (B6) mice exhibited elevated plasma corticosterone (CORT) levels, whereas \textit{Per2} mutant mice did not display a similar response. B6 mice, but not \textit{Per2} mutant mice, increased alcohol drinking gradually during restraint and remained slightly elevated following restraint. In addition, potential mechanisms may involve methylation of \textit{Per2}, and suppression of \textit{Per2} and \textit{POMC} in the hypothalamus, which may result in alterations in HPA axis function and propensity for stress associated addictive behaviors, including alcohol consumption. Thus, these data point towards an involvement of \textit{Per2} in the effects on the mechanisms mediating stress-induced alcohol drinking.

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**Per genes and addiction**

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Over the last decade, clock genes have shown to be modulating various behavioral and pharmacological effects of drugs of abuse (i.e. cocaine, morphine, alcohol). For instance, we formerly provided evidence for a specific and differential involvement of the clock genes *Per1* and *Per2* in the development of cocaine-induced behaviors. Subsequently, we further investigated the involvement of *Per* genes in the development of morphine dependence. We could reveal the involvement of the gene *Per2* in the development of morphine-induced tolerance and withdrawal as observed by lowered degree of tolerance and attenuated withdrawal signs in morphine-treated *Per2<sup>Brdm1</sup>* mutant mice. In contrast, *Per1<sup>Brdm1</sup>* mutant mice did not exhibit any significant difference in degree of tolerance and withdrawal signs as compared to their wild-type littermates. However, as previously observed for cocaine, the presence of a functional *Per1* gene appeared to be crucial in the development of morphine-induced sensitization and conditioned place preference. With regard to alcohol, we previously showed an enhanced consumption of alcohol in *Per2<sup>Brdm1</sup>* mutant mice as compared to controls, and a specific implication of this gene in the circadian regulation of central alcohol sensitivity. Most recently, we also revealed the involvement of other key clock components the CK1e/d kinases, responsible for regulating PER proteins availability, in driving alcohol relapse. CK1e/d inhibitor treatments indeed strongly diminished or even prevented alcohol deprivation effect in long-term alcohol drinking rats. Altogether, these results reveal the importance of *Per* genes in modulating the effects of various drugs of abuse.

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Assessing the role of delta opioid receptors in reinforcement processes: reward or learning?

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Within the endogenous opioid system, mu opioid receptors are necessary for most drugs of abuse to exert their rewarding properties. Data from pharmacological and gene knockout approaches have suggested that delta opioid receptors might play a similar role. Yet, a major difficulty when assessing drug reinforcement in animal models lies in the tight intertwining of reward and learning processes. We hence tested the hypothesis that delta receptor inactivation might affect drug reinforcement by altering learning rather than reward.

We showed that delta opioid receptor knockout (Oprd1⁻/⁻) mice display impaired appetitive (morphine) and aversive (lithium) place conditioning, which can be restored, however, by providing additional non-spatial cues. In contrast, these mice show intact acquisition of morphine self-administration as compared to wild-type (WT) counterparts, and reach similar, or even higher, break-points. Thus the reinforcing and motivational properties of morphine are maintained, if not increased, in Oprd1⁻/⁻ mice, whereas the ability to form drug-context associations is blunted. These data suggest preserved or even facilitated striatal function but altered hippocampal function in mutant animals. We verified these hypotheses by investigating cognitive performance of Oprd1⁻/⁻ mice and WT controls in several striatum- and hippocampus-dependent tasks. Together, these results shed new light on the role of delta opioid receptors in reinforcement processes and the balance of striatal and hippocampal activities. Interestingly, they also stress the difficulty of drawing robust conclusions regarding the hedonic value of a drug using a classical paradigm of conditioned place preference in genetically modified animals.

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Dysfunction of glutamatergic neurons and altered response to alcohol in the infralimbic cortex following a history of dependence

WH Sommer, M Meinhardt, S Perreau-Lenz, M Heilig, AC Hansson, R Spanagel

In experimental rodents a prolonged history of alcohol dependence persistently up-regulates voluntary alcohol consumption and behavioral stress responses. While this phenotype is primarily mediated by amygdala hyperactivity, there is emerging evidence for a critical role of the medial prefrontal cortex (mPFC) in the inhibition of addictive behaviours. The underlying neurobiology of altered mPFC function is poorly understood.

A step-wise transcriptome analysis strategy pointed us to the infralimbic projection neurons as a critical point of dependence related neuroplasticity. We identified several candidate genes including transcription factors and the metabotropic glutamate receptor type 2 (Grm2) that are robustly and persistently downregulated during ethanol abstinence and are associated with alterations in glutamatergic neurotransmission. By rescuing the expression of these genes in infralimbic neurons we are able to block behavioural responses that emerged during the development of dependence.

Together, these data point towards profound alterations in mPFC function, in particular within the infralimbic region, and predict dysfunction of inhibitory control over behaviour in alcohol addiction. We discuss our findings within the current theories on reward learning and extinction.

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Measuring rewarding effects of drugs in mice and humans

Dai Stephens

Although it is commonplace to assert that drugs are taken because they are rewarding, this statement is rather circular. Human studies rely heavily on subjective reports of drug-induced reward, while animal studies are reliant on interpretation of behaviours that we assume measure similar processes to those that human subjective reports address. However, there is little evidence that different measures of reward in animals relate to similar mechanisms, nor that they relate to human reports. One approach to obtaining translational data in this area is to use tests in animals and humans that are homologous. Conditioned reinforcement refers to the acquisition of reinforcing properties by neutral cues repeatedly paired with primary reinforcers. We have developed a method to study conditioned reinforcement in human subjects and are using it to investigate whether genetic manipulations that alter conditioned reinforcement in mice have counterparts in humans. Since the phenomenon of conditioned reinforcement has strong theoretical links with the cue-induced reinstatement model of relapse to drug taking in abstinent individuals, such methods may offer a way to study homologous behaviours in humans and animals, and bring together cross species studies of behavioural genetics.

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Ethanol reward and aversion in a high drinking selected mouse line

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The High Drinking in the Dark (HDID) line of mice has been selectively bred for high blood ethanol concentrations following the Drinking in the Dark test and is a genetic model of binge-like drinking. HDID mice drink to intoxication during a limited access procedure and tend to drink in larger bouts than the genetic control stock. Differences in voluntary ethanol intake may be related to differing sensitivity to the motivational effects of ethanol, either rewarding or aversive. Previous studies of selected lines and inbred strains have shown a strong negative genetic relationship between home cage drinking and ethanol-conditioned taste aversion. Less consistently seen is a correlation between voluntary ethanol consumption and ethanol-conditioned place preference. This pattern has been demonstrated in the HDID mice, which show a blunted ethanol-conditioned taste aversion relative to unselected controls, while not demonstrating consistent differences in ethanol-conditioned place preference. These findings suggest that the binge-like drinking of the HDID line may be related to a weakened sensitivity to ethanol's aversive effects, rather than an altered perception of ethanol reward.

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Executive dysfunction in *parkin* null mice.

EO Akano¹ & MP McDonald²

In addition to motor symptoms, more than half of Parkinson's patients have cognitive manifestations such as impairments in short-term memory, attention, and impulsivity. However, there is a paucity of scientific data on cognitive deficits in mouse models of Parkinson disease. The purpose of this study was to determine whether mice lacking the *parkin* gene exhibit the “executive” dysfunction characteristic of Parkinson's disease. We trained these mice and age-matched wild-type littermates on a 3-hole serial reaction time task commonly used to assess sustained attention, but modified to include indices of impulsive behavior. At baseline, using a 1-s cue duration, there was no significant difference in accuracy (hits) across genotype. Reaction time and hopper latencies were slower in the *parkin* null mice compared to controls. On sessions with pseudo-randomized shorter cue durations (0.25-1.0 s), the *parkin* knockouts had significantly fewer hits and significantly slower reaction times than wild-type controls. During a probe session using variable intertrial intervals, the *parkin* null mice had fewer hits as well as increased premature responses, indicating impaired attention and increased impulsivity. This study showed that knocking out the *parkin* gene results in deficits in fronto-striatally-mediated executive tasks. This suggests that the *parkin* knockout mice can be used to study cognitive manifestations of Parkinson disease as well as therapeutic interventions against these symptoms.

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Poster Session

Poster #2

Genome-wide gene expression analysis from monozygotic twins discordant for the nicotine metabolic ratio identifies WDFY1 as a negative regulator of nicotine metabolism.

Andrew W Bergen1, Aaron Wacholder1, Denise M Nishita1, Gary E Swan1

Monozygotic (MZ) twin biospecimens enable epigenetic research, as MZ twins share 100% of their genome and epigenome at the moment of twinning, and accumulate differences thereafter. The Nicotine Metabolic Ratio (NMR), the ratio of two stable metabolites of nicotine, cotinine and 3’hydroxycotinine, is associated with cigarette consumption, response to transdermal nicotine smoking cessation treatment, and carcinogen activation and level. Adjustment for clinical covariates and CYP2A6 genetic variation suggests additional biological factors. Four MZ twin pairs (never smokers, female, aged 29-58 years), with plasma NMR differences >2 SD than the mean twin plasma NMR difference, were selected from a sample of 39 twin MZ pairs. Genome-wide gene expression analysis of lymphoblastoid cell line RNA was performed using the Affymetrix Gene ST 1.1 Array. QC metrics were monitored using RNA integrity number analysis and Expression Console software. Background correction, quantile normalization and summarization were performed using the RMA algorithm and the ComBat algorithm was applied to adjust for batch effects. Replicates were averaged and analyzed using a two-class paired test, revealing a single gene significantly differentially expressed (lower in the high-NMR individuals), WDFY1 (chr2q36.1), with a FDR of 12.5%, the minimum possible in the study design. The mouse homolog, Wdfy1 (chr1qC4), has been identified as differentially expressed in multiple mouse genome wide gene expression datasets in strains defined by differences in alcohol consumption with decreased expression in the high alcohol consuming strain (prior to alcohol consumption). The WD repeat and FYVE domain containing 1 gene product may be a negative regulator of alcohol consumption and nicotine metabolism in mice and man, respectively.

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Poster #3
Neural circuitry of social play: Involvement of septal vasopressin and GABA

R Bredewold1, CJ Smith1, AH Veenema1

Social play is an affiliative and rewarding behavior that is displayed by nearly all mammals and peaks at juvenile age. Social play is essential for the normal development of social behavior and is impaired in social disorders like autism. We aimed to investigate the neural circuitry of social play. The vasopressin system within the lateral septum modulates neural responses to a variety of social stimuli. Moreover, recent in vitro studies suggest that vasopressin interacts with GABA interneurons in the lateral septum. To study the involvement of septal vasopressin and GABA in the regulation of social play, single-housed 5-week-old juvenile male rats were exposed in their home cage to a sex- and age-matched unfamiliar rat for 10 min. Administration of the specific vasopressin V1a receptor antagonist (CH2)5Tyr(Me2)AVP into the lateral septum enhanced social play. Administration of vasopressin into the lateral septum had no effect on social play, despite the strong anxiogenic effect of vasopressin when rats were tested on the elevated plus-maze. Blockade of V1a receptors did not change anxiety-related behavior of rats exposed to the elevated plus-maze. Finally, we showed that the increase in social play after administration of a V1a receptor antagonist was blocked by co-administration of the GABA receptor agonist muscimol. Together, these findings demonstrate an important role for vasopressin in the regulation of social play likely by interacting with GABA in the lateral septum.

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Poster #4
Preliminary evidence for telomere length as a marker of neurodevelopment.

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Telomere length represents a promising biomarker that implicates a mechanistic biological pathway linking early adversity and negative health outcomes, including alterations in neurocognitive development. Early adversity, including severe social deprivation as a result of institutional care, has been also associated with alterations in neurodevelopment. In Bucharest Early Intervention Project, the first randomized controlled trial of foster care compared to continued care in institutions we have demonstrated both alterations in EEG power and alterations in telomere length. To test the hypothesis that telomere length is a biomarker of the impact of early adversity on neurodevelopment, and provide insight into a potential mechanism, we examined the association between EEG power and genetic vulnerability with telomere length in this unique study population. Identification of these biological mechanisms is crucial to our understanding of the impact of early adversity. SIRT1, a member of the Sirtuin family of proteins, is a histone deacetylase involved in plasticity, neuronal differentiation and also implicated in telomere length dynamics. We therefore examined the association between telomere length, EEG power and SIRT1 rs3758391 (c/c vs. c/t and t/t) genotype. DNA and EEG power (age 8) were available on participants (N=57) children, 30 in the foster care intervention group (FCG) and 27 in the continued institutional group (CAUG). Controlling for group designation (FCG vs. CAUG) and age at which DNA was collected we determined that SIRT1 genotype interacted with EEG absolute beta power (occipital p<0.004, parietal p<0.008, central p<0.02 and frontal p<0.03) to predict telomere length. This is the first study to our knowledge to examine the association between telomere length and EEG power, and to examine the impact of genetic variations in genes known to regulate telomere length and response to stress. This provides initial evidence that telomere length maybe associated with neurodevelopmental trajectories that are altered by early adversity.

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Poster #5
Mouse strain differences in induction of chronic depressive-like behavior

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Depression is projected to become the second most common cause of disability in the world in a few years. Although heritability estimates suggest genetic factors account for approximately 40% of the risk for the development of depression, the genetic underpinnings remain largely unknown. Research on depression strongly relies on animal models approximating important aspects of the clinical pathology, including both acute and chronic models. Chronic models are believed to have higher face and construct validity for depression than acute models, however, the most commonly used chronic models require long induction periods and are difficult to be established in a reliable fashion, thus impractical for genetic studies. Here, we used a validated depression model in which mice were subjected to short daily swims for a week to induce chronic depression. We compared the depression-like phenotypes in five mouse strains including C57BL/6J, DBA/2J, A/J, CBA/J and Balb/cJ. The immobility time during the swimming test in the final day were significantly increased in C57BL/6J, DBA/2J and Balb/cJ mice (p<0.05), compared to the first day. In contrast, over the days of swim, the CBA/J strain mice showed almost no immobility and the A/J strain mice maintained the medium level of immobility. Since increased immobility following repeated forced swim is associated with other key depressive signs, it can be used as an index of depression. These preliminary results provide the foundation for further dissection of genes that influence individual's vulnerability to depression.

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Poster #6
GeneWeaver: An integrative repository and tool set for functional genomic studies of neurobehavioral disorders

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Genetic mapping, gene expression analysis and mutation screens provide broad based gene functional characterization, but confidence in individual observations is low, and aggregating evidence from multiple sources is technically challenging. The main reason is that most data are not stored in readily computable forms, and for those that are, disparate data types and data resources render integrative analyses problematic. We have developed a web-based software system that integrates a curated database of functional genomics experimental data with an interactive tool set to enable rapid integration of large numbers of genomics experiments. The system enables rapid refinement of positional candidates from mapping studies, and offers many other applications that enable users to share and compare gene set centered data. In our project to curate and analyze the alcohol and addiction literature, we find that much of the aggregate evidence implicates a role for genes that have not previously been associated with these traits. The data model is being expanded to incorporate additional data types. A major challenge to information aggregation is data sparsity as a consequence of the uneven landscape of experimental results. Our system is intended to enhance group and public data sharing to improve the density of gene set data around problems of specific interest. Increased data density will enable users to integrate information across behavioral disorders and related neurobehavioral phenomena.

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Poster #7
Forward genetic screen of mutant zebrafish for altered nicotine and varenicline responses

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Smoking and alcohol abuse are often coincident, with 90% of heavy drinkers also smokers, making smoking the greatest health risk in these patients. The most efficacious pharmacotherapeutic used to treat tobacco dependence is varenicline, a characterized α4β2 nicotinic acetylcholine receptor partial agonist and nicotine antagonist. Despite its success, a subset of patients fails to respond to varenicline treatment. This may be attributed to individual genetic variations linked to the nAChR binding or alternative modes of action.

To test this possibility we are using a larval zebrafish nicotine locomotor activation assay that we have shown robustly detects attenuation of the locomotor response by varenicline. Using this behavioral assay, we initiated a forward genetic screen of zebrafish mutants generated in our laboratory via a gene-breaking transposon (GBT) containing a protein trap (pGBT-RP2.1). We have a current catalogue of 360 mutants, over 100 of which show neurally localized expression of the mutated gene.

We have preliminarily identified mutant-line GBT 136 as having a substantially attenuated nicotine locomotor response. We are characterizing the gene involved and will be investigating its importance in the clinical treatment of tobacco dependence. We are also screening 11 GBT lines with habenular-localized expression patterns. The habenula is a conserved brain region recently shown to be involved in regulation of nicotine self-administration in mammals. Here we summarize our habenula gene screen, the results of which may provide important clues needed to elucidate the mechanisms associated with nicotine consumption and varenicline efficacy.

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Poster #8
Potential role of nicotinic acetylcholine receptors in regulating response to restraint stress in mice.

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The response to a psychological stressor, such as restraint, is determined by the activity of the hypothalamic-pituitary-adrenal (HPA) axis and in the induction of immediate early genes such as c-fos. Nicotinic acetylcholine receptors (nAChR) are a diverse set of ligand gated ion channels that are distributed throughout the central and peripheral nervous systems, including regions of the HPA axis. The effects of subunit gene deletion will be used to evaluate the role of nAChR subtypes as potential regulators of response to restraint stress. Although the nAChR subtypes are diverse, known receptors in the nervous system require the expression of β2 or β4 structural subunits or α7 ligand binding subunit. Therefore, the effects of deletion of each of these genes will be evaluated. A pilot experiment has been conducted with C57BL/6 mice (background strain for each null mutant). Mice were subject to restraint for 0, 5, 10, 15, 30 and 60 min. Blood samples were taken to measure serum levels of ACTH and corticosterone. Brains were sectioned for measurement of c-fos mRNA. Both ACTH (4-fold increase) and corticosterone (7-fold increase) were elevated by the first time point and remained elevated throughout the test period. mRNA encoding c-fos showed distinct differences in regional expression and time course for response to restraint stress. Some cortical regions and hippocampus achieved maximal increases in c-fos by 5 min. Other cortical regions and olfactory bulbs required 15 min to attain maximum response. These experiments establish an appropriate time to examine effects of nAChR gene deletion.

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Poster #9
Interactions between thermoregulatory challenge and antidepressant drugs on behavior

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Major depressive disorder is characterized by dysfunction of thermoregulation, including elevated diurnal rhythms of core body temperature and decreased sweating, while antidepressants of diverse pharmacological profiles induce sweating as a clinical side effect, and clinical recovery is associated with normalization of thermoregulatory function. Together, these data suggest that the pathophysiology of depression as well as antidepressant drug action may involve interactions with thermoregulatory pathways. To test the hypothesis that these two pathways are interlinked, we used an acute subthreshold (subthreshold for induction of antidepressant-like behavior) injection of the SSRI citalopram paired with exposure to warm ambient temperature. We found that citalopram, by itself, induced hyperthermia that was comparable to that induced by exposure to increased ambient temperature (37°C) for 85 min. Neither citalopram by itself, nor exposure to increased ambient temperature induced antidepressant-like effects in the forced swim test. However, when rats were both treated with citalopram and exposed to elevated ambient temperature, they experienced an exaggerated hyperthermia, and responded with antidepressant-like behavior (increased swimming) in the forced swim test. In addition, the core body temperature immediately prior to the forced swim test predicted the amount of antidepressant-like behavior (r = 0.648; p < 0.00008). These data provide a rationale for novel therapeutic strategies for the treatment of affective disorders, including development of novel antidepressant drugs that interact with thermoregulatory pathways.

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Poster #10
Changes in hippocampal \textit{Bdnf} mRNA expression due to voluntary ethanol consumption and voluntary exercise in mice.

TM Darlington, JD Segall, RA Rodman, MA Ehringer

Prior research has revealed a relation between natural reward seeking behavior and drugs of abuse at the behavioral and neurobiological levels (Nestler, 2005). Our laboratory recently reported that in C57Bl/6J mice, preference for alcohol decreases when there is an exercise wheel present (Ehringer et al. 2009). Exercise has been shown to both increase neurogenesis (Dishman et al. 2006) and protect against the neurodegenerative effects of binge alcohol (Leasure and Nixon, 2010), so we hypothesized that changes in Brain-derived neurotrophic factor (\textit{Bdnf}) would correlate with access to voluntary ethanol consumption, voluntary wheel running, both, or neither. Adult female C57Bl/6J mice were housed individually in one of four cage conditions: empty with water, empty with alcohol and water, running wheel with water, or running wheel with alcohol and water. After 16 days, mice were sacrificed and hippocampal tissue was collected. Total RNA was extracted, reverse transcribed, and TaqMan® probes were used for real-time quantitative PCR with an endogenous control (\textit{Actnb}). Results indicate an overall effect of cage condition on hippocampal expression of \textit{Bdnf} (p=0.01). While there is no difference in \textit{Bdnf} expression in drinking mice (p=0.1), exercising mice had increased expression compared to controls (p=0.02) and to drinking mice (p=0.001). This increase in \textit{Bdnf} due to exercise was completely attenuated when both exercise and ethanol were present (p=0.37). Results from this research should provide improved understanding of the neurobiology of alcohol use and exercise, and suggests hippocampal function is involved in mediating interactions between rewarding behaviors.

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Poster #11

High-throughput phenotyping of the Knock-Out Mouse Population

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The Knock-Out Mouse Project (KOMP) and International Knockout Mouse Consortium (IKMC) have generated a comprehensive set of targeted ES cell lines covering the mouse genome. Ascribing phenotypic consequences to these perturbations is the effort of an international consortium, including several centers in the United States (KOMP2). ES cells are imported from a central repository and reanimated at The Jackson Laboratory for production of test mice and C57BL/6N controls in the same facility. Phenotypic characterization of large numbers of mouse stocks must focus on high-level, broad screens conducted in multiple-test batteries. The Jackson Laboratory Neurobehavioral Phenotyping Protocol balances large-scale testing with resolution aimed at characterizing mice sufficiently to suggest follow up directions. Briefly, a modified SHIRPA battery assesses basic neurological function, and includes dysmorphology, sensory response and grip strength. A second week of testing includes activity, anxiety-like and exploratory behaviors, followed by behavioral despair and locomotor coordination. Ophthalmoscopy and electroretinography are performed to assess eye development and function. A week long sleep study is performed. Acoustic startle response, pre-pulse inhibition, auditory brainstem response, and seizure threshold are also assessed. Physiological screens including hematology, plasma chemistry, growth and body composition complement these neurobehavioral assays. Mice are reared in environmentally controlled conditions, and a regular stock of C57BL/6N is tested weekly to evaluate drift in these conditions. Knock-out mouse phenotypes are identified based on the entire population of knockout lines, and relative to temporally-matched pooled controls. All data are delivered to the Data Coordinating Center at the EBI for worldwide distribution.

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**Poster #12**  
Depressive-like phenotype in male mice after two weeks of nicotine treatment

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Cigarette smoking has long been associated with depression, but has mainly been interpreted as a form of self-medication. Recent evidence, however, suggests that smoking itself may increase the risk of developing depression. We hypothesized that chronic nicotine causes both a depressive-like phenotype and an imbalance of serotonergic gene expression in the dorsal raphe nucleus (DR), the main source of brain serotonin (5-hydroxytryptamine; 5-HT). To test this hypothesis we treated adult male mice with vehicle (0.9% saline, n=7), 6.3 mg/kg nicotine (n=7), or 24 mg/kg nicotine (n=8) per day for 14 days, using subcutaneous (s.c.) osmotic minipumps. Nicotine dependence and the mice’s stress coping behavior in the forced swim test (FST) were assessed. Brains were analyzed for mRNA expression levels of slc6a4 (encoding the 5-HT transporter, SERT), htr1a (encoding the autoinhibitory 5-HT₁A receptor) and tph2 (encoding tryptophan hydroxylase 2, TPH2, the rate-limiting enzyme for brain 5-HT synthesis) using in situ hybridization histochemistry. A challenge s.c. injection of 0.5 mg/kg nicotine on day 13 confirmed successful treatment; all nicotine-treated mice responded with an attenuated decrease in rectal temperature relative to vehicle-treated controls. Compared to controls, mice of the high-dose group also displayed less bodyweight and depressive-like behavior (less swimming, more immobility) in the FST on day 14, and left less fecal boli in the swim tank. No treatment effect on slc6a4 or htr1a mRNA expression was found, while tph2 expression remains to be analyzed. We conclude that two weeks of nicotine treatment are sufficient to cause a depressive-like phenotype in mice.

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Poster #13
Opioid Sensitivity in Mice Selectively Bred to Consume or Not Consume Methamphetamine

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Genetic factors likely influence individual susceptibility to escalating MA use. Replicate mouse lines were produced that consume high (MAHDR) or low (MALDR) amounts of MA in a two-bottle choice MA drinking (MADR) procedure. Selective breeding was used to aggregate risk alleles in one line and protective alleles in the other. Quantitative trait locus (QTL) analysis identified a QTL on mouse chromosome 10 in both sets of lines, mapping near the mu-opioid receptor (MOP-r) gene, Oprm1. MALDR mice have greater expression of Oprm1 than MAHDR mice in the medial prefrontal cortex. To examine differences between the lines in opioid system sensitivity, the magnesium sulfate abdominal writhing test was used. The MADR lines did not differ in sensitivity to the analgesic effects of the MOP-r agonist, fentanyl, consistent with results from other nociception tests. To assess differences in avidity for opioids, morphine drinking was measured. MALDR mice consumed more morphine than MAHDR mice in a two-bottle choice morphine drinking study, using a saccharin fading procedure. These data are consistent with previous results for morphine versus quinine drinking. Finally, because MALDR mice exhibit higher Oprm1 expression, naltrexone, a MOP-r antagonist, was hypothesized to enhance drinking; however, this result was not obtained. We speculate that extreme avoidance of MA by the low line may provide an explanation. These results support a negative genetic correlation between the consumption of MA and opioids and support additional consideration of Oprm1 as a candidate gene that influences differences in MA consumption between the MADR lines.

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Poster #14
Song choice according to female movement in Drosophila males

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Mate selection is critical to ensuring the survival of a species. In the fruit fly, Drosophila melanogaster, genetic and anatomical studies have been done for decades on the mate recognition and corresponding courtship initiation, as a model system for the study of neural control for behavioral decision-making of the males. Much less is known, however, how the courtship quality is controlled in a temporally dynamic manner and how the male performance is assessed by a female for her decision to accept copulation.

Here, we report that the courting male dynamically adjusts the relative proportions of the song components, pulse song or sine song, according to female locomotion. Males deficient for olfaction failed to perform the locomotion-dependent song modulation, indicating that olfaction provided information regarding proximity to the target female. This olfactory mutant males also showed lower copulation success when paired with wild-type females, suggesting that the temporal song control of the males served as courtship strategy to increase mating receptivity of the females.

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**Poster #15**  
**Glutamatergic Gene Expression in Postmortem Hippocampus from Alcoholics and Cocaine Addicts**

M.-A. Enoch1; Z. Zhou1; D.C. Mash2; Q. Yuan1; D. Goldman1.

This study's aim was to detect changes in glutamatergic gene expression that might be specific to chronic alcohol or drug exposure or common to the addictive process. We focused on the hippocampus, a constituent of the memory/conditioning neuronal circuitry of addiction.

Using RNA-Seq we quantified mRNA transcripts in postmortem total hippocampus from 8 alcoholics, 8 cocaine addicts and 8 controls, all male. An analysis was undertaken of the 28 genes expressed in the hippocampus that encode glutamate ionotropic (AMPA, kainate, NMDA) and metabotropic receptor subunits, together with glutamate transporters.

The alcoholics showed FDR corrected (p < 0.05) up-regulation of six genes relative to controls and cocaine addicts: *GRIA4* (encoding the AMPA subunit GluA4); *GRIK3* (kainate subunit GluR7); *GRIN2D* (NMDA subunit GluN2D); and *GRM1*, *GRM3* and *GRM4* (metabotropic subunits mGluR1, mGluR3 and mGluR4 respectively). *GRIN2B* (encoding NMDA subunit GluN2B) was up-regulated (p = 0.008) in both alcoholics and cocaine addicts. Unique to cocaine addicts was down-regulation of *GRIN3A* that encodes the NMDA receptor subunit GluN3A. Finally, *SLC1A3*, encoding the glutamate transporter EAAT1 was down-regulated in the alcoholics.

In hippocampus, the effect of chronic alcohol exposure was largely to up-regulate genes encoding all four groups of glutamate receptors. Cocaine had more limited effects. In contrast, a similar analysis of GABAergic pathway genes (Enoch et al., PLoS ONE, 2012) revealed both specific and common effects of alcohol and cocaine exposure on multiple genes, predominantly down-regulation. These opposing effects might be expected since glutamate and GABA are respectively the major excitatory and inhibitory neurotransmitters.

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Poster #16
Abnormal social behavior and social recognition but normal anxiety in 5xFAD transgenic mice

TJ Flanigan 1, SK Rao 1, L Dantzler 1, MP McDonald 1,2

The 5xFAD mouse model of Alzheimer’s disease exhibits robust age-related neurodegeneration in the subiculum and cortical layer V pyramidal neurons. A recent study reported reduced anxiety on the elevated plus maze in the 5xFAD mice, which increased with age. We replicated the published effect but found that the time on open arms did not reflect decreased anxiety, i.e., a greater tendency to enter the open arms. Instead, it was explained in part by the tendency of wild-type mice to habituate to the closed arms, and in part by aversive vibrissal overstimulation in the transgenics when contacting the walls of the closed arms. When whiskers were snipped, 5xFAD mice did not avoid the closed arms. Wild-type mice of this background strain exhibited home-cage whisker-barbering behavior, but 5xFAD mice did not. In our experience failure to barber is associated with submissiveness and reduced social activity. However, the 5xFAD mice had significantly more social behaviors and were not submissive to the identified dominant wild-type from other cages. Home-cage recordings revealed significantly higher social behaviors in the transgenic mice in nearly every category. On the other hand, 5xFAD mice demonstrated a deficit in social recognition at both 90 minutes and 24 hours following an initial exposure to an unfamiliar juvenile mouse. These social behavior phenotypes in the 5xFAD transgenics may be the result of degeneration in the subiculum, which mediates social behavior, and layer V cortical neurons, which exert tonic inhibition on neurons in the barrel cortex associated with vibrissal sensation.

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Poster #17  
**Human CHRNA3/B4 Intergenic Single Nucleotide Polymorphism (SNP) rs8023462 alters gene expression *in vitro***

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The cluster of human neuronal nicotinic receptor (nAChR) genes (*CHRN*) on the long arm of human chromosome 15 (15q25.1) has been associated with a variety of smoking and drug-related behaviors. In particular, a single nucleotide polymorphism (SNP), rs8023462, located in the intergenic region between *CHRNA3* and *CHRNB4*, is associated with early initiation of alcohol and tobacco use. We used a promoter-driven luciferase expression assay in cell culture to determine whether this SNP changes gene expression *in vitro* using human lung cancer cell lines (H69, H82 and H446) as well as cell lines with neuronal characteristics (SH-SY5Y (human neuroblastoma) and PC12 (rat pheochromocytoma)). No differences in gene expression were detected between major and minor allele constructs when human lung cancer cell lines were transfected. However, differences in gene expression due to SNP were noted in both SH-SY5Y and PC12 cells. Specifically, differentiated SH-SY5Y cells transfected with minor allele constructs showed a significant decrease in gene expression compared to those transfected with the major allele construct (p<0.05, n=16), while undifferentiated PC12 cells had increased gene expression when transfected with the minor allele constructs, relative to major allele constructs (p=0.005, n=22). Data from these experiments support the hypothesis that SNPs within the intergenic region of *CHRNA3/B4* may affect gene expression in neurons. This work is an important first step in identifying regulatory regions within the cluster that may be involved in alcohol and tobacco use.

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Poster #18
Acute functional tolerance to ethanol in mice selectively bred for high and low alcohol preference drinking

BM Fritz, NJ Grahame, SL Boehm II

Propensity to develop acute functional (or within session) tolerance to alcohol (ethanol) may influence the amount of alcohol consumed, with higher drinking associated with greater acute functional tolerance (AFT). The goal of the current study was to assess this potential correlated response in second and third replicate lines of mice selectively bred for high (HAP2&3) and low (LAP2&3) alcohol preference drinking. We predicted that HAP mice would develop greater AFT to alcohol’s ataxic actions than LAP mice. Male and female HAP2&3 and LAP2&3 mice were tested for development of AFT on a static dowel task. This task requires that animals maintain balance on a wooden dowel in order to prevent falling. On test day, each mouse received one (1.75g/kg; experiment 1) or two (1.75g/kg and 2.0g/kg; experiment 2) injections of ethanol; an initial administration before being placed on the dowel and in another experiment, an additional administration after the first regain of balance on the dowel. Blood samples were taken immediately after loss of balance and regain in Experiment, 1 and after first and second regain in Experiment 2. It was found that HAP mice fell from the dowel significantly earlier and at lower BACs than LAP mice following the initial injection of ethanol and were therefore more sensitive. Furthermore, the single-injection experiment detected significantly greater AFT development (BAC2-BAC1) in HAP mice as compared to LAP mice, supporting our hypothesis. This study illustrates the rapidity with which adaptive pharmacodynamic processes can take place which may contribute to excessive alcohol consumption.

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The SNP rs1948, associated with early nicotine and alcohol use, may alter the expression of the CHRNA5/A3/B4 cluster of genes

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Many human genetics studies have shown the importance of the CHRN genes in nicotine and alcohol dependence phenotypes. Our lab has shown an association between SNP rs1948, located in the 3'-UTR of CHRNA4, and early age of initiation for both tobacco and alcohol use. The present study examines whether the risk variant of rs1948 is associated with differences in gene expression using an in vitro model. To address this aim, two constructs of different lengths (0.8kb, 1.7kb) containing the rs1948 were generated and then cloned in a pGL3-Promoter vector upstream and downstream of the luciferase reporter gene. Three different mammalian cell lines (B35, N2A, and SH-SY5Y) were transfected with each construct. Luciferase assays were performed to assess gene expression at 48-h and 96-h (undifferentiated and differentiated cells) post-transfection time points. Results revealed different allelic effects on luciferase expression due to the length of the construct, suggesting the presence of interacting regulatory elements in the region. Most of the same allelic effects were observed when cells were transfected with constructs cloned either up or downstream of the luciferase gene. Interestingly, the overall luciferase expression increased when cells were transfected with constructs cloned upstream of luciferase but was reduced when cloned downstream, suggesting that the expression of α3 and β4 could be regulated oppositely. Overall, the results demonstrate that the risk allele of rs1948 could play a role in the age of initiation for tobacco and alcohol use by modifying the expression of some of the subunits located in this cluster of genes.

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Poster #20

Using allele-specific expression analysis to identify cis-eQTLs and parent-of-origin effects in reciprocal F1 crosses of LG/J and SM/J mice.

NM Gonzales 1, S Gopalakrishnan 1, CD Bryant 1, J Pritchard 1, AA Palmer 1,2.

We have been successful in mapping QTLs for a variety of behavioral and physiological traits in a 34th generation advanced intercross between LG/J and SM/J mice. In order to ascribe specific genes to these QTLs we are developing a database of eQTLs, some fraction of which are expected to co-map with our library of QTLs. We will discuss our use of Next-generation sequencing to detect cis-eQTLs and parent-of-origin-specific expression differences in reciprocal F1 crosses of LG/J and SM/J mice. By using RNA-seq to measure gene expression in the brains of genetically identical heterozygotes that differ only by the direction of the parental cross, we can simultaneously identify allele-specific and parent-of-origin effects on gene expression. These studies will be useful as we develop additional eQTL data using association mapping in conjunction with RNA-seq data from our advanced intercross lines, which is now at generation 48. We hope that the convergence of QTL and eQTL data will allow us to develop high quality, testable hypotheses about the roles of specific genes in a variety of traits.

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Harnessing pain heterogeneity and RNA transcriptome to identify blood-based pain biomarkers: a correlational study in a graded chronic constriction injury model.

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Neuropathic pain is a major clinical problem, partly because a mechanism-based diagnosis is not yet available to supplant empirical treatment decisions. These problems may be alleviated by objective, mechanism-based biomarkers. However, there are few candidates and none are clinically accepted to date. Based on the premise that peripheral and central immunity underlie neuropathic pain mechanisms, we hypothesized that blood-based biomarkers could be discovered in rats by integrating graded chronic constriction injury (CCI), pain behavior, ipsilateral lumbar dorsal horn (iLDH) and whole blood transcriptomes, and pathway analysis. The integrated correlational analysis yielded two putative biomarker gene panels, with many of these genes encoding for proteins with a recognized role in immune or nociceptive mechanisms. These genes were validated in a subsequent prospective trial. Bioinformatic pathway analysis of the iLDH transcriptome also identified Fc\textgreekgamma and Fc\textepsilon signaling pathways, which is of potential significance for neuropathic pain mechanisms. Furthermore, the distribution of previously published ‘pain genes’ was identified within the iLDH transcriptome. Concordant genes were predominantly upregulated following nerve injury, suggesting that allodynia severity is generally associated with recruitment of new genes and processes, rather than downregulation of existing ones. We are the first to use the transcriptome to identify putative blood-based biomarker panels in a rodent model of nerve injury, and similar approaches may be used to develop biomarkers for other CNS diseases. Future prospective qualification studies may demonstrate the applications of this putative biomarker panel in neuropathic pain patients, as the first generation of objective, blood-based pain biomarkers.

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Copy number variations (CNVs) are emerging as an important genomic cause of several common neurodevelopmental disorders (Sebat et al, 2007; Walsh et al, 2008; Mefford et al, 2008; Stefansson et al., 2008). Recently, deletions within the neurexin 1 gene (NRXN1; 2p16.3) have been found in cases with autism, mental retardation and schizophrenia (Kirov et al., 2008; Feng et al, 2006; Zahir et al, 2007). Furthermore, NRXN1 CNVs that disrupt exons were found to be significantly associated with schizophrenia with a high odds ratio (P = 0.0027; OR 8.97, 95% CI 1.8-51.9; Rujescu et al., 2008). A neurexin 1α knockout mouse (Nrxn1tm1Sud) already exists and has been used to analyse the role of neurexins in synapse formation and some behaviours (Etherton et al., 2009) within a mixed genetic background. The Nrxn1tm1Sud knockout is an ideal model of the human CNV as it disrupts exon one of the alpha-isoform, as do the majority of human disease-associated deletions. We have backcrossed the Nrxn1tm1Sud mice and performed the first behavioural phenotyping of these mice in a pure genetic background using a battery of tests that span the behavioural domains known to be affected in neurodevelopmental disorders, such as anxiety, cognition and social behaviour (Kas et al, 2007). Such an approach with a diverse behavioural test battery will enable us to fully explore the behavioural consequence of such a deletion, revealing a possible impairment in the traits related to neurodevelopmental disorders. The development of behavioural 'end-points' will also allow the use of this mouse as a model of neurodevelopmental disorders and a tool to study possible interventions and/or treatments.

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Poster #23
Evaluation of cognitive deficits in the MPTP mouse model of Parkinson’s disease

LC Gregg\(^1\) and MP McDonald\(^1\)

Parkinson’s Disease is one of the most common neurodegenerative diseases, affecting an estimated four to six million people worldwide. The symptoms are predominately due to the degeneration of dopaminergic cells in the substantia nigra, causing a reduction in dopamine in the striatum and fronto-striatal pathway. Parkinson’s disease is mainly associated with motor deficits, yet there are cognitive deficits that occur during the course of the disease in more than half of patients. The cognitive deficit manifests as impairment in fronto-striatal executive function, with deficits in attention, speed of mental processing, impulsivity, and short-term working memory. Many studies have examined the motor symptoms in mouse models of Parkinson’s disease, but executive dysfunction in a mouse model of Parkinson’s disease has not been reported. We are examining the cognitive changes in mice using the subchronic MPTP model of Parkinson’s disease. Our version of the subchronic regimen involves five daily injections of 18 mg/kg over 5 consecutive days. MPTP damages the nigro-striatal and fronto-striatal pathways to induce slowness, rigidity, tremors, postural instability and possibly impairment in executive function. A 3-hole serial reaction time (SRT) task was used to measure sustained attention, but modified to include indices of impulsivity. Wild-type mice were trained on the SRT task before MPTP injections. Five days following the final MPTP injection, mice began SRT testing to measure the effects of MPTP on sustained attention. Given that MPTP reduces fronto-striatal dopamine, we expect to show that MPTP impairs attention and increases impulsive behavior in this on-going study.

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Poster #24

Frustrating access to a running wheel increases EtOH self-administration in mice: influence of sex and b-endorphin

Judith E. Grisel, Lauren J. Bowser & Carlos Piza-Palma

Exercise mitigates psychopathological states related to stress. Excess alcohol drinking has also been linked to stress. The purpose of these studies was to investigate the influence of voluntary running on oral self-administration of alcohol (EtOH). Because b-endorphin has been implicated in the effects of exercise as well as the causes of drinking, we tested C57BL/6J mice, along with transgenic mice possessing varying levels of b-endorphin, for oral self-administration of EtOH during free and blocked access to a running wheel. Subjects had ad lib access to food and water in a home cage that also contained a running wheel. EtOH was available in a 20% solution for 2 hr/day beginning 3 hr into the dark cycle. After 5 days of evaluating EtOH consumption and preference under these conditions, a 10-day experimental period ensued in which wheel rotations were prevented for 3 hr on alternate days beginning 1 hr before and continuing for the 2 hr during EtOH availability. Locking the wheels resulted in increased drinking depending upon both sex and b-endorphin. Despite similarly robust running in all subjects, females, but not males, consumed more EtOH on days when the running wheel was blocked. Moreover, b-endorphin appeared to mediate this increase as self-administration on wheel-blocked and wheel-free days did not differ in opioid deficient mice. Limiting access to an appetitive running wheel, and therefore preventing the opportunity for voluntary exercise, appears to selectively increase the motivation to drink in female mice, suggesting sex-differences in the behavioral and neural influences on alcohol consumption.

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Poster Session

Poster #25

JP Gyekis\textsuperscript{1}; MA Dingman\textsuperscript{2}; AR Revitsky\textsuperscript{2}; BP Bryant\textsuperscript{3}; DJ Vandenbergh\textsuperscript{1,2}; ME Frank\textsuperscript{4}; DA Blizard\textsuperscript{1}

Drinking solutions of various drugs is a convenient research method for high-throughput mouse genetics studies. While the goal is usually to evaluate pharmacologic effects of those drugs, sensory factors can often play an important role. In the case of nicotine consumption, gustatory, trigeminal, and olfactory factors could influence acceptance of the oral solutions, but little work has been done to investigate them. We used lithium chloride injections paired with the oral consumption of 150 μg/ml nicotine to condition taste aversion (CTA) in 3 inbred mouse strains: C57BL/6J, DBA/2J, and 129X1/SvJ. Then mice were then given access to bitter, sour, sweet, salty, and several irritant solutions (one solution per day) to test whether the aversion generalized to these tastes. We also tested for generalization to the odor of nicotine. Nicotine CTA generalized to the bitter stimulus quinine hydrochloride and the chemosensory irritant spilanthol in all strains. In C57BL/6J mice, nicotine CTA generalized to hydrogen peroxide (an activator of TRPA1), and in DBA/2J the aversion generalized to the olfactory cue of nicotine. These findings suggest that the trigeminal irritation, olfactory stimulation, and bitter taste of nicotine can all influence mouse behavior and encourage further work to characterize strain differences in sensory response to orally consumed drugs between strains.

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Bayesian estimates of genetic handedness predict oscillatory asymmetries.

Roeland Hancock¹,²

Non-right personal and familial handedness has been sporadically associated with altered patterns of functional brain asymmetry and numerous psychiatric disorders that often occur with atypical lateralization. Binary (right/non-right) familial hand preferences were reported by approximately 4000 probands and Gibbs sampling was used to estimate additive genetic effects under a multifactorial threshold model. In contrast to prior attempts to classify individuals based on familial handedness, this approach makes minimal assumptions regarding the genetic nature of handedness, provides a continuous measure and avoids confounding family size and handedness.

The results support the existence of a moderately heritably genetic component to handedness, with a posterior heritability estimate of 22.8%-36.4% (95% highest posterior density), consistent with independent estimates obtained from twin studies. The model also supported independent sex and familial effects (14.2%) but not parental effects. Estimated latent trait and additive genetic values for probands were highly predictive of electroencephalographic (EEG) power spectra and interhemispheric connectivity, validating the method's utility for generating an experimentally useful measure. These pedigree-based estimates are proposed to be a reliable proxy for genetic factors that can account for a considerable portion of individual variability in functional cerebral asymmetry in both normal and psychiatric populations.

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Poster #27
Effects of Sodium Butyrate on Methamphetamine Sensitized Locomotor Activity

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Neuroadaptations associated with behavioral sensitization induced by repeated exposure to methamphetamine (MA) appear to be involved in compulsive drug pursuit and use. Increased histone acetylation, an epigenetic effect resulting in altered gene expression, may promote sensitized responses to psychostimulants. The role of histone acetylation in MA-induced locomotor sensitization was examined by measuring the effect of inhibiting histone deacetylase with sodium butyrate (NaB) on expression and acquisition of sensitization. For the effect on expression, vehicle or NaB (630 mg/kg, ip.) was administered 30 min prior to MA challenge in mice treated repeatedly with MA (10 days of 2 mg/kg MA) or saline (10 days) and then locomotor response to MA challenge was measured. NaB treatment increased the locomotor response to MA in both acutely MA treated and sensitized animals. For acquisition, NaB was administered 30 min prior to each MA exposure (10 days of 1 or 2 mg/kg), but not prior to the MA challenge test. Treatment with NaB during the sensitization acquisition period significantly increased locomotor activation in sensitized mice only. NaB alone did not significantly alter locomotor activity. Acute NaB or MA, but not the combination, appeared to increase striatal acetylation at histone H4. Repeated treatment with MA, but not NaB or MA plus NaB, increased striatal acetylation at histone H3. Although increased histone acetylation may alter the expression of genes involved in acute locomotor response to MA and in the acquisition of MA-induced sensitization, results for acetylation at H3 and H4 showed little correspondence with behavior.

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Poster #28
Widespread failure to replicate human candidate gene studies of amphetamine sensitivity

AB Hart1, H de Wit2, AA Palmer12

Humans vary in their responses to d-amphetamine, and this variation is heritable. Sensitivity to the subjective effects of a drug may predict its abuse liability; therefore, genetic variation underlying subjective responses may also influence drug abuse risk. We have previously reported genetic associations with several genes and responses to d-amphetamine in 99-162 healthy, non-drug abusing volunteers. Participants received d-amphetamine (10 or 20 mg) or placebo in randomized order and completed self-report questionnaires (POMS, DEQ, ARCI) at regular intervals. We observed significant associations with the following genes: ADORA2A, BDNF, COMT, CSNK1E, DRD2, FAAH, SLC6A2, SLC6A3, and SLC6A4. More recently, we have attempted to replicate these findings in 219-282 new participants, tested using the same procedures. None of the 11 previously observed associations replicated, strongly suggesting that the initial findings were false positives. One possible explanation for the preponderance of false positives in our prior studies may be failure to completely account for multiple testing within and between these studies. Our results have broad implications for human candidate gene studies that use small sample sizes. In conclusion, our data suggests the need for a paradigm shift away from small, likely-underpowered candidate gene studies to identify genetic variants underlying psychiatric and other complex phenotypes.

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Poster #29
A Novel Model of Oral Nicotine Intake to Achieve Rapid, High Consumption in Mice

William Horton¹,², Lori Frazier¹, Hannah Gissel¹, Vivian Nyugen¹, Jerry Stitzel¹,²

Smoking continues to be the leading cause of preventable death and disease in the United States. To treat chronic smokers, it is critical to understand the neurobiology underlying this addiction. Despite several decades of research, these chronic neurochemical effects are not completely understood. One of the difficulties in studying these effects is that currently available mouse models of oral consumption have several limitations. First, to achieve high-doses of nicotine intake a gradual ramping procedure is required which makes some studies infeasible. Second, to mask the bitter taste of nicotine 2% saccharin has typically been used. Even with this masking, at high-concentrations of nicotine, overall fluid intake is typically half that of normal animals which introduces the potential confound of dehydration. To resolve these limitations, we have developed a novel paradigm that allows for high nicotine consumption while still maintaining a normal fluid intake. As a proof of concept, C57BL/6J mice were examined in this procedure and achieved on average 45-60 mg nicotine/kg body weight/day while still consuming an average of 6.5 mL fluid/day. These doses are achieved in less than a week, removing the need for long ramping procedures. Furthermore, we have measured precipitated conditioned place aversion (CPA) with mecamylamine to determine if these concentrations are sufficient to induce aversion.

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SNPs in the putative promoter region of \textit{CHRNB3} have been repeatedly associated with tobacco behaviors including: nicotine dependence, subjective response to nicotine, quit attempts, and cigarettes per day. Previously our lab has shown that the 3kb region upstream of this gene influences the expression of a reporter gene, specifically the major allele haplotype causes increased expression compared to the minor allele haplotype. In the current study we have expanded on these initial findings by altering three SNPs in this region (rs13277254, rs6474413, and rs4950) to determine if they influenced reporter gene expression. Constructs were designed that had the major or minor haplotype with the alleles flipped (eg. minor allele on major haplotype background) at the three SNPs located directly upstream of the luciferase reporter gene. Constructs were tested in the SH-SY5Y human neuroblastoma and HEK 293T human embryonic kidney cell lines. In both SH-SY5Y and HEK 293T cells the major haplotype led to higher luciferase gene expression compared to the minor haplotype, but this difference was no longer significant when the allele at rs6474413 was reversed. Additionally, in the HEK 293T cells rs13277254 appeared to modulate this response. These data suggest that certain SNPs upstream of \textit{CHRNB3} may be involved in regulating gene expression, but this may be cell type specific. Future work will focus on examining transcription factors predicted to bind to DNA regions containing these SNPs, to determine whether allelic variation affects their ability to bind. This work contributes to our understanding of the molecular mechanisms that may underlie the human genetic associations between variation in this region and tobacco behaviors.

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SNPs in promoters of miR-9 genes in alcoholics can alter binding of transcription factors

NS Kinstlinger, Y Wang, L Tejeda, M Garbarini, O Anees, AZ Pietrzykowski

microRNAs are small, non-coding, RNA molecules that act as very powerful regulators of mRNA and protein expression. Alcoholism is a multigenic disorder of unclear molecular underpinnings. Using animal models, we showed the essential role of miR-9 in the development of molecular tolerance to alcohol. Here, we wanted to establish the involvement of miR-9 in the development of alcoholism in humans. People have three miR-9 genes located on distinct chromosomes and embedded within host genes. We used 282 DNA samples from the COGA (the Collaborative Studies on Genetics of Alcoholism) collection to search for alcoholism-related SNPs in each of the six genomic regions related to miR-9. We sequenced two ~3,000 nucleotide long regions per each miR-9: one containing a particular miR-9 gene and its proximal promoter, the other containing a distal promoter of the respective host gene. We detected the presence of approximately 150 SNPs. Interestingly SNPs were absent from the miR-9 stem loop regions but many were found in the promoter regions. SNPs in a promoter can change the binding of transcription factors and subsequently gene expression. Using MAPPER2 we found that several SNPs are capable of altering the binding affinity of different transcription factors expressed in neurons. Together, described changes in the binding of transcription factors to miR-9 promoters may alter basal or stimulated expression levels of miR-9, leading to faster development of drug tolerance in alcoholics.

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Wild-derived mouse strains exhibit large variation of home-cage activity among strains. The aim of this study is to elucidate the genetic basis of strain difference in home-cage activity. The wild-derived mouse strain MSM/Ms (MSM) exhibits higher activity in the home-cage than C57BL/6 (B6), a commonly used laboratory strain. We have analyzed consomic strains derived from B6 and MSM to elucidate genetic mechanism responsible for strain differences in the regulation of home-cage activity. Nearly half of the consomic strains showed significant difference in home-cage activity compared to B6. In order to identify a causative gene related to different level of home-cage activity, we focused on one of the chromosomes, Chr6. A QTL analysis using F2 progeny which were made between consomic strain of Chr 6 and B6 revealed QTL for home-cage activity on distal region of Chr6. One of the sub-consomic strains, which has a large chromosomal region (38 Mbp), showed significantly low level of home-cage activity. However, analyses of further recombinants (sub-consomic strains) clearly showed that this region comprises a cluster of QTLs for home-cage activity, thus two QTLs increase activity and two other QTLs reduce activity. Further analysis of one of the four QTLs revealed that a short segment (~3.2 Mbp) from MSM exhibited higher home-cage activity and only five annotated genes are reported in this QTL region. Our study showed that QTL can be dissociated into more QTLs with different effects on the phenotype. Thus, the results illustrated complex nature of genetic basis for complex traits.
Poster #33
Silencing of Wfs1 gene in HEK cells induces pathways related to the neurodegeneration and mitochondrial damage

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WFS1 gene produces protein with unknown actions but its functional deficiency causes different neuropsychiatric and neuroendocrine syndromes. In the present study we aimed to find the functional networks influenced by the time-dependent WFS1 silencing in HEK cells. We performed whole genome gene expression profiling (Human Gene 1.0 ST Arrays) 24, 48, 72 and 96 hours after transfection of HEK cells with three different WFS1 siRNAs (siRNA1, siRNA2 and siRNA3). Negative control siRNA (NC) and cells without transfection were used as controls. In order to verify the silencing we performed QRT-PCR and western blot analysis. Two different approaches were used for analysis. First we analyzed the overall effect of the siRNA treatment on the gene expression profile. As a next step we performed time-course analysis separately for different siRNAs and combined for all siRNAs. QRT-PCR and western blot confirmed clear silencing of the WFS1 gene expression after 48 hours. Eleven genes had FDR value less than 10% and most of them are genes related to the mitochondrial dysfunction and apoptosis. Time-course analysis confirmed significant correlation between the WFS1 silencing and changes in the gene expression profiles. The pathways that were influenced significantly by the WFS1 silencing were related to the mitochondrial damage and neurodegenerative diseases. Our findings suggest the role of WSF1 gene in the cell survival and its involvement in the degenerative diseases.

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Sensitization to the psychomotor (locomotor) stimulant effects of abused drugs is thought to be a genetically regulated phenomenon representing an increase in the positive motivational effects of these substances following repeated exposure(s). However, we know very little about the heritability of this phenomenon or the extent to which similar genes regulate sensitization to different drugs of abuse. The goal of this study was to determine if those genes regulating sensitization to the stimulant effects of alcohol (ethanol) also regulate sensitization to the stimulant effects of cocaine. Lines of mice bred for high (HLS) and low (LLS) locomotor sensitization to ethanol were given repeated exposure to cocaine or saline and alterations in locomotor activity were monitored. Consistent with previous observations, there were marked differences in general locomotor activity between lines with HLS animals displaying consistently higher locomotion than LLS animals following saline injections. There were no consistent differences between lines in either the acute or the sensitized locomotor responses to cocaine; both lines showed robust stimulation and sensitization. Furthermore, there were no differences in ethanol-induced locomotor activity between animals sensitized to cocaine and those given repeated saline injections (controls); this null effect was consistent between lines. These data suggest that those genes that regulate locomotor sensitization to ethanol are distinct from those regulating locomotor sensitization to cocaine.

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High-precision QTL mapping of complex behavioral traits in the Diversity Outbred mouse population

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Complex trait analysis, systems genetics, and QTL mapping are powerful integrative approaches to the identification of genetic variants that influence behavioral traits, but current strategies are limited due to low genotypic and phenotypic diversity. New genetic reference and mapping populations promise to improve the study of complex behavioral traits. We have been developing and characterizing advanced mouse populations, including the new Collaborative Cross (CC) and Diversity Outbred (DO) populations. The DO is a heterogeneous stock derived from the same five common and three wild-derived founders as the CC. The high genetic diversity of the founders and outbred breeding scheme produces genetically unique mice with high recombination density, which is ideal for mapping causative loci. High-throughput behavioral phenotyping of the DO mice (G4-5, n=300) consisted of the open-field, light-dark box, tail-suspension, and visual-cliff assays, from which ~50 traits were subject to QTL analysis and positional candidates were identified for corresponding intervals. Phenotypic variation dramatically exceeded that of the BXD Recombinant Inbred lines and approximated that of the CC lines. Genetic analysis revealed high-precision QTL (1-3 Mb) with some containing a single gene. Most intervals can be narrowed further using haplotype differentiation. Several QTL overlapped with previously published loci, and novel loci were found for anxiety- and depression-related traits. In many cases, QTL were specific to wild-derived lines, reflecting the added value of the increased genetic diversity of the DO to behavioral genetics. Our results demonstrate that in a single conventional sized mapping population, the DO enables high precision complex trait analysis.

The Jackson Laboratory, Bar Harbor, ME, USA; Supported by GM076468 and The Jackson Laboratory
**Poster #36**

Isolation-rearing during adolescence followed by re-socialization alters behavioral responses to social defeat in adulthood in association with altered functional responses of serotonergic neurons in the dorsal raphe nucleus of male rats.

Lukkes JL¹, Burke AR¹, Long MT¹, Armijo LM¹, Hale MW¹,², Lowry CA¹.

Social isolation of male rats during adolescence followed by re-socialization with other isolates increases anxiety states and alters activity of stress-related serotonergic systems in adulthood. Here, we extended these studies to also investigate the effects of post-weaning social isolation on reactive versus proactive coping styles in response to social defeat (SD) in adulthood. In addition, we investigated how isolation-rearing followed by subsequent SD in adulthood affects serotonergic neurons in the dorsal raphe nucleus (DR) using dual immunohistochemical staining for c-Fos and tryptophan hydroxylase. Juvenile male rats were reared in isolation or groups of three for a 3-week period from weaning to mid-adolescence, after which, rats were re-socialized either with the same rearing condition (group with group (G-G), isolate with isolate (I-I)) or with subjects of a different rearing condition (group with isolate (G-I), isolate with group (I-G)) for an additional 2 weeks until adulthood. Increased anxiety-like behavior in the social interaction test and increased reactive emotional coping behaviors in the SD paradigm were observed only in I-I rats compared to G-G rats. In all treatment conditions, SD increased c-Fos expression in serotonergic neurons in several subregions of the DR. The re-socialization factor also altered several of these measures. These data suggest that adolescent social isolation, as well as re-socialization, alters the effects of stress-related stimuli on behavior and serotonergic systems, which have been implicated in the pathophysiology of stress-related psychiatric disorders.

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Poster #37
Selectively bred crossed High Alcohol Preferring (cHAP) mice demonstrate acute intoxication and develop functional tolerance during free-choice access to ethanol

LM Matson 1, A Buckingham 1, E Tombers 1, NJ Grahame 1

cHAP mice, selectively bred from a cross of HAP1xHAP2 replicate lines, achieve high (~250 mg/dl) blood ethanol concentrations (BECs) during free-choice ethanol access. Here we assessed whether cHAP mice become intoxicated during their first 12 hours of access, and also if functional tolerance to ethanol-induced ataxia develops following chronic ethanol exposure. In experiments 1 and 2, 12 mice had access to 10% ethanol and water; an additional 12 had water-only access. In experiment 1, bi-hourly readings were taken on day 1 of ethanol access during the dark portion of a 12:12 cycle. Once ethanol mice reached an intake rate of ≥1.5 g/kg/h, it (and a sex-matched water mouse) was tested for number of footslips on a balance beam and blood-sampled to assess BEC. In experiment 2, after 3 weeks ethanol access, mice were given a 1.75 g/kg injection of 20% ethanol, tested for number of footslips, and blood-sampled to assess BEC. In experiment 1, 10 of 12 ethanol-drinking mice met the intake criterion, with an average BEC of 103 mg/dl, and also had more footslips than water mice (p < .05). In experiment 2, ethanol-exposed mice had fewer footslips than ethanol-naïve mice (p < .05), demonstrating tolerance. These studies demonstrate that cHAP mice drink to intoxication during acute ethanol access, and develop functional tolerance to the ataxic effects of ethanol following chronic exposure. Therefore, the cHAP line may be a unique genetic model for studying both acute and chronic excessive ethanol intake.

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Poster #38
Functional significance of netrin-G1 and netrin-G2 in differential brain circuits: insight from physiologic and behavioral studies in KO mice.

Hiroshi Matsukawa¹, Hiromichi Goto¹, Rafael Luján², Sachiko Akiyoshi-Nishimura¹, Qi Zhang¹, Kunio Yaguchi¹, Tsutomu Hashikawa¹, Ryuichi Shigemoto³, Shigeyoshi Itohara¹

Netrin-G1 and netrin-G2, vertebrate-specific membrane-anchored members of the UNC-6/netrin family, are preferentially distributed on distinct axons in the brain, and determine the selective distributions of their receptors, NGL1 and NGL2, within specific sub-dendritic segments of target neurons in a cortical layer-specific manner (Akiyoshi-Nishimura et al., PNAS, 2007). The physiologic roles of these transneuronal ligand-receptor interactions, however, are poorly understood. Here, we performed electron microscopic and electrophysiologic analyses of the hippocampal CA1 region, in which netrin-G1/NGL1 and netrin-G2/NGL2 interactions occur along the distal temporoammonic pathway (TA-CA1) and the proximal Schaffer collateral pathway (SC-CA1), respectively. Immuno-electron microscopy revealed the localization of netrin-Gs and NGLs along the excitatory presynaptic and postsynaptic membranes, respectively, of the selective pathways. The absence of netrin-G1 or netrin-G2 led to alterations in theta-burst evoked long-term potentiation and post-tetanic potentiation in opposite directions in a circuit-specific manner: attenuated TA-CA1 synaptic plasticity in netrin-G1 knockout (KO) and augmented SC-CA1 synaptic plasticity in netrin-G2 KO, without alterations of the basal synaptic properties. We further observed differential phenotypes of these KO mice in a wide range of behavioral domains, including cognition, emotionality, sensory, and motor functions. Remarkably, there was almost no phenotypic overlap between these KO mice. These findings indicate that the trans-synaptic netrin-G/NGL interactions play important roles in modulating the synaptic efficacy of specific neuronal circuits and behavioral output.

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Poster #39
Chrna4 polymorphisms negatively associated with nicotine dependence show altered nicotinic receptor expression and function measured in vitro.

TD McClure-Begley1, RL Papke3, C MD Isaacson3, MR Kimbrell3, P Xie1,2, J Gelernter1,2, MR Picciotto1

Tobacco use represents a leading cause of preventable death across the globe. In spite of the efforts of public health authorities and the advent of several pharmacological interventions designed to curb and alleviate nicotine dependence, decline in tobacco use has stagnated. Here we report the biological characterization of several missense polymorphisms identified in human current nonsmokers that appear cumulatively to protect against the development of nicotine dependence (ND) (Since each variant was rare, effects of individual variants on risk could not be evaluated; statistical evidence showed that they are protective when binned together; but it is also the case that specific variants could be neutral or even increase risk for ND). Receptor activation was examined following expression of six alpha4 variants in xenopus oocytes with the endogenous agonist acetylcholine, as well as with nicotine. Acetylcholine was equipotent across the 6 alpha4 variants examined, but the pharmacological parameters calculated for nicotine differed markedly across the putatively-protective alpha4 variants. This finding suggests that altered receptor function conferred by the polymorphisms is unique to the actions of nicotine, and would not be expected to affect normal cholinergic neurotransmission in nonsmoking carrier individuals. When expressed transiently in HEK293 cells, the cumulatively-protective alpha4 variants show a gene-dose-dependent alteration in receptor assembly and surface expression as measured by [3H]-epibatidine binding and mAb270 labeling in a cell-adherent ELISA assay, respectively. Further experiments are being designed to provide the mechanisms responsible for the observed effects and generate new, more effective therapeutic targets for nicotine dependence.

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NIH DA14241
Recent studies have identified bidirectional interactions between alcohol intake and the circadian timing system at both the physiological and molecular-genetic levels. For example, selective breeding for high and low ethanol preference drinking results in co-selection for circadian phenotype in both mice (Hofstetter et al. 2003) and rats (Rosenwasser et al. 2005). In the present studies, we characterized light-entrained and free-running circadian activity rhythms in mice selectively bred for other ethanol-related phenotypes that might be more closely associated with excessive ethanol intake. Experiment 1 employed a newly developed mouse line selected for high binge-like drinking to intoxication in the “drinking in the dark” test (HDID-1 mice) and their genetically heterogeneous HS/Npt controls, while Experiment 2 compared lines of mice selectively bred for high (withdrawal seizure prone, WSP-2) and low (withdrawal seizure resistant, WSR-2) sensitivity to ethanol withdrawal. Under a normal light-dark cycle, high ethanol-responsive HDID-1 and WSP-2 mice both displayed relatively less activity in the early night and relatively more activity in the late night compared to their low-responsive counterparts. Under free-running conditions, WSP-2 mice showed significantly longer free-running periods than WSR-2 mice, while in constant light, HDID-1 mice showed significantly shorter free-running periods than HS/Npt mice. Taken together with previous studies, these results show that selective breeding for diverse responses to ethanol results in co-selection for circadian phenotype, and strengthen the evidence for genetic linkages between circadian clock function and ethanol responsiveness. Further work will be required to identify the specific physiological mechanisms mediating these relationships.
Poster #41
Examination of SNPs in GABRA2 in a longitudinal sample for and alcohol abuse and dependence

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It has been established that \(\gamma\)-aminobutyric acid (GABA\(_A\)) receptors are affected by ethanol in animal models (Dildy-Mayfield 1995). Human GABRA2 genetic variants have also been associated with alcohol abuse and dependence in several studies (Enoch 2008).

The current report investigated five single nucleotide polymorphisms (SNPs) in GABRA2 in families from two ongoing studies; the Colorado Center on Antisocial Drug Dependence (CADD) and the Genetics of Antisocial Drug Dependence (GADD) (Stallings 2003; Stallings 2005). A total of 2,496 subjects from the CADD and 2,965 subjects from the GADD were genotyped. Adolescent Caucasian subjects were analyzed from a combined clinical and community-based sample of adolescents and adults with available genotypic and phenotypic data to test for association with a DSMIV alcohol abuse and dependence symptom sum score. For clinical subjects, this phenotypic measure was age- and sex-corrected based on the distribution in the community sample. A family based association test was performed using FBAT (Rabinowitz and Laird 2000). No association with the alcohol abuse and dependence symptoms with either sample was found (\(p > 0.05\)).

Because the GADD and CADD are longitudinal studies, subjects have been assessed for several behaviors across multiple waves of data collection. Based on the hypothesis that adolescents have not had time to develop substance abuse problems, we plan to examine conduct disorder symptoms in wave 1 of data collection and subsequently assess alcohol behaviors in wave 2 of data collection in both samples. This expanded analysis may provide insight into the developmental nature of alcohol use disorders.

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Poster #42
Effects of chronic nicotine treatment on tolerance and receptor regulation in beta4 nAChR mice

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Chronic nicotine treatment in mice can cause both tolerance to nicotine and an upregulation in epibatidine. We chronically treated beta4 wildtype (+/+), heterozygous (+/−), and null mutant (−/−) mice with nicotine doses of 0, 0.5, 1.0, 2.0, and 4.0 mg/kg/hr for 10 days. Animals were tested for tolerance with an acute dose of 0, 0.25, 0.5, 0.75, 1.0, or 1.5 mg/kg. Y-maze, open field, and body temperature results were measured. The beta4 null mutant mice developed tolerance at all chronic doses, particularly in measures of body temperature. Heterozygous mice also developed tolerance greater than that of wildtype mice, although not as great as null mutants. Total epibatidine binding and binding with either cytisine or A85380 was performed in the cortex, thalamus, hindbrain, superior colliculus, inferior colliculus, olfactory bulb, medial habenula, and interpeduncular nucleus. Cytisine sensitive epibatidine binding (primarily alpha4beta2) increased with increasing chronic dose across all regions and genotypes. Thus, deletion of the beta4 subunit did not affect upregulation of the alpha4beta2 receptor. Cytisine-resistant binding significantly decreased for null mutants and heterozygotes in all regions except cortex, thalamus, and superior colliculus. There is virtually no residual binding in the A85380-resistant population in the null mutants, and binding was significantly reduced in the the heterozygotes. In conclusion, chronically treated mice lacking the beta4 subunit show increased tolerance to nicotine-induced hypothermia, and a decrease in cytisine-resistant and A85380-resistant epibatidine binding, but with no alteration in response of alpha4beta2 nAChR to chronic treatment.

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Poster #43

Genetic and pharmacological manipulation of hippocampal acetylcholinesterase activity provides a novel model of depression

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Previous studies have shown that blockade of acetylcholinesterase (AChE) induces symptoms of depression in human subjects. These studies suggested that increasing cholinergic tone in humans could contribute to the etiology of major depressive disorder. Consistent with this possibility, limiting the activity of nicotinic and/or muscarinic acetylcholine receptors can have antidepressant-like effects in animal models and have been shown to decrease symptoms of depression in clinical trials in human subjects. To evaluate whether increasing cholinergic tone may provide a novel model of depression in mice, we blocked AChE in male C57BL/6J mice by systemic physostigmine administration and found this resulted in a dose-dependent increase in depression-like behaviors. These effects were reversed by administration of the SSRI antidepressant fluoxetine as well as by administration of a nicotinic or muscarinic antagonist. Fluoxetine administration also caused an increase in AChE activity in the brain, with the greatest change observed in the hippocampus. We therefore administered physostigmine or shRNAs targeting AChE directly into the hippocampus and found increased anxiety- and depression-like behaviors, and decreased resilience in the social defeat model. These phenotypical alterations were partially rescued by co-infusion of a shRNA-resistant AChE transgene in the hippocampus. These data suggest that hippocampal ACh is an important modulator of behaviors related to depression. We therefore propose that shRNA-mediated knockdown of hippocampal AChE represents a new model for the study of depression-like endophenotypes. Further, changes in the (hippocampal) cholinergic system may be critical in mood disorder and a specific endophenotype in depression.

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Poster #44
Effects of β-endorphin on social play in adolescent mice

VA Moser¹, JE Grisel¹

Social interactions in general, and social play in particular, are necessary for normal development. Depriving animals of social play leads to abnormal development, as well as social and cognitive deficits in adulthood. Previous research has evidenced a role for endogenous opioids in social play: antagonists decrease, and β-endorphin infusions increase, social play in adolescent rats (Trezza, Damsteegt, Achterberg, & Vanderschuren, 2011). The present study was aimed at further elucidating the neural substrates of social play by examining a range of associated behaviors in transgenic mice that vary in their capacity to synthesize β-endorphin. Naïve, adolescent mice were paired with a sex- and genotype-matched partner and their interactions were videotaped and analyzed for 30 min. Contrary to expectations, our results indicate that decreasing levels of β-endorphin are associated with more social play. In addition, male and female pairs engaged in equivalent amounts of play behavior. Thus, our results support robust social play behavior in male and female mice that is not dependent upon β-endorphin. In light of previous findings and a growing appreciation for the critical role of social play in normal development, these data suggest that the neural circuitry of social play may be multifaceted and the role of β-endorphin not straightforward.

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Poster #45
Rapid extinction of cocaine CPP in C57BL/6J mice from running: interference with consolidation or learning enhancement?

ML Mustroph1, 2, 4, DS Miller 1, 3, D Sohn 1, 3, & JS Rhodes 1, 3, 4

Exercise is a potential intervention for drug addiction because it generates brain plasticity that may be used to help abolish drug associations. Our previous study established that voluntary exercise promotes extinction of conditioned place preference (CPP) for cocaine if exercise is made available after conditioning, but the mechanisms by which this occurs are not known. This study will test two possible explanations for how exercise might extinguish CPP. One possibility is that plasticity generated from running, including new hippocampal neurons, facilitates learning that drug is no longer associated with context during CPP testing in which animals experience the previously drug-paired context in the absence of drug. An alternate explanation is that running interferes with the initial consolidation of the drug-to-context learning. To arbitrate between these alternatives, the experiment was repeated with a time delay lasting 30 days before or after 30 days of running between the 4 cocaine conditioning trials, which were always administered first, and CPP testing which was always administered last. We reasoned that if plasticity from running enhanced new context learning, then by placing a sufficient time delay after exercise, plasticity should return to baseline and the effect of exercise should be eliminated, i.e., extinction in CPP should appear similar in runners and sedentary animals. On the other hand if exercise interferes with consolidation, then the 30 day delay before but not after running, should abolish the effect of exercise on extinction of CPP. Results help clarify the mechanism by which exercise after conditioning weakens drug-to-context associations.

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**Poster #46**  
The ADNFLE β2V287L mutation in the β2 nicotinic acetylcholine receptor alters nicotine tolerance in mice

HC O’Neill¹, PA Herder¹, EE Meyers¹, SR Grady¹ and MJ Marks¹

The major neuronal subtypes of nicotinic acetylcholine receptors (nAChR) is the heteromeric α4β2 subtype. Mutations in the channel-lining M2 region of α4β2 nAChR, found in some human ADNFLE cases, can impact receptor function. Mice with the β2 valine-to-leucine point mutation (β2V287L) show increased sensitivity to nicotine in measures of locomotion and hypothermia. We sought to determine if the β2VL mutation changed tolerance to challenge doses of nicotine following either chronic infusion or acute pre-exposure. For acute studies, β2VL wildtype (WT), heterozygous (HT), and mutant (MT) mice received a dose of saline or nicotine (0.025 mg/kg, ip) and 10 minutes later received a challenge dose of saline or nicotine (0.25 mg/kg, ip) and were assessed for changes in nicotine sensitivity. Following acute exposure, HT and MT mice tolerated 0.25 mg/kg challenge dose if they received a prior dose of 0.025 mg/kg nicotine. For chronic studies, β2VL WT, HT, and MT mice received nicotine at maximum tolerable doses (4.0 mg/kg for WT; 0.4 or 1.0 mg/kg for HT and MT) or saline by chronic intravenous infusion for 10 days. After chronic treatment, β2VL WT mice show tolerance to 0.5 or 1.0 mg/kg of nicotine. β2VL HT and MT mice showed no tolerance to 0.4 mg/kg nicotine. The data suggest receptors with the β2VL mutation may have a different response to chronic treatment, perhaps in desensitization states. Acute data indicate that behavioral desensitization can be attained with very low nicotine doses.

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Poster #47  
Two genetic loci control syllable sequences of ultrasonic courtship vocalizations in inbred mice

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The ultrasonic vocalizations (USV) of courting male mice are known to possess a phonetic structure with a complex combination of several syllables. The genetic mechanisms underlying the syllable sequence organization were investigated. This study compared syllable sequence organization in two inbred strains of mice, 129S4/SvJae (129) and C57BL6J (B6), and demonstrated that they possessed two mutually exclusive phenotypes. The 129S4/SvJae (129) strain frequently exhibited a “chevron-wave” USV pattern, which was characterized by the repetition of chevron type syllables. The C57BL/6J strain produced a “staccato” USV pattern, which was characterized by the repetition of short-type syllables. An F1 strain obtained by crossing the 129S4/SvJae and C57BL/6J strains produced only the staccato phenotype. The chevron-wave and staccato phenotypes reappeared in the F2 generations, following the Mendelian law of independent assortment. These results suggest that two genetic loci control the organization of syllable sequences. These loci were occupied by the staccato and chevron-wave alleles in the B6 and 129 mouse strains, respectively. Recombination of these alleles might lead to the diversity of USV patterns produced by mice.

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Poster #48

Transgenerational epigenetic effects of lead exposure on behavior in Drosophila melanogaster

Elizabeth K. Peterson, Helen Ghiradella, Bernard Possidente, and Helmut Hirsch

Environmental exposure to lead has been shown to have severe effects on cognition (Banks et al, 1997; Bellinger, 2008; Lanphear et al, 2000; Lanphear et al, 2005; Jusko et al, 2008), sexual development (Wu et al, 2003; Wolff et al, 2008), and fertility (Gennart et al, 1992) in humans. In Drosophila melanogaster, developmental lead exposure alters synaptic (He et al, 2009) and behavioral development (Hirsch et al, 2003); the latter is associated with changes in gene expression (Hirsch et al, 2009). In wild type Canton-S D. melanogaster, preliminary research has shown that maternal exposure to lead decreases fecundity in unexposed offspring (P< 0.05). However, the long-term, multigenerational implications of living in a lead polluted environment are not understood. In addition, our knowledge of the evolutionary significance of epigenetic changes is limited, particularly when pollutants in the environment induce them. To study the transgenerational epigenetic effects of lead exposure, parental populations of a recombinant inbred line of D. melanogaster was reared from egg stages until adult day 5 in either control medium (0 μM PbAc) or experimental medium (250 μM PbAc). Two mating conditions (1: Control Male X Control Female; and 2) Control Male X Experimental Female) were used to generate three generations of offspring reared in control medium. Fecundity was measured in the third generation of offspring by counting the total number of viable offspring produced by each female in each group. There was a significant increase (P < 0.05) in fecundity when females in the parental generation were exposed to lead. This pilot provides evidence that lead induces transgenerational epigenetic effects on fecundity; it is currently being replicated to further delineate the mechanisms underlying this long-term epigenetic change.

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Poster #49
Common co-expression networks of alcohol-related genes in mice and men.

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Transcriptomes are organized into modules of co-expressed genes that can be explained by known biological concepts, such as genomic location, functional group or cell type. Here, we used a Weighted Gene Co-expression Network Analysis (WGCNA; Zhang and Horvath, 2005) to compare the transcriptional organization of human and mouse brains and identify molecular networks and individual genes associated with high alcohol consumption in the two species. We first obtained microarray data from two data sets: a) transcriptomes of 32 postmortem human brains including 17 alcoholics and 15 control cases and b) whole brain transcriptomes of 42 BXD (C57BL/6J X DBA/2J) recombinant inbred mouse strains and used separate WGCNAs to partition transcriptomic variance into biologically meaningful gene co-expression modules. We then compared the two modular networks and identified modules highly overlapping between the species, i.e., modules containing many of the same genes. This analysis revealed a cross-species meta-network of highly overlapping modules, suggesting that brain transcriptomes in humans and mice are regulated by similar mechanisms. Detailed examination of the genes from the overlapping modules showed that many genes were up-regulated in human alcoholics and alcohol-preferring mice (based on Mulligan et al., 2006), suggesting some common mechanisms underlying alcohol consumption in human alcoholics and mouse models of excessive drinking. An over-representation analysis of the alcohol-related genes highlighted two functional groups: chromatin modifications and glutamateergic synapse, suggesting that these biological processes play a central role in regulation of alcohol consumption in multiple species.

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**Poster #50**

γ neurons are the gateway for DA input to mushroom body during aversive olfactory memory formation

Hongtao Qin1, Michael Cressy1,2, Wanhe Li1,3, Jonathan Coravos4, Stephanie Izzi2 and Josh Dubnau1

In *Drosophila*, Mushroom Bodies (MBs) are the site of CS-US association for olfactory memory. MBs receive olfactory CS inputs from cholinergic projection neurons and dopamine (DA) neurons convey the aversive US. We demonstrate that US information is received solely by the γ lobe subset of MB neurons. This is surprising given the known role in memory of signaling within additional MB cell types. Convergent evidence has demonstrated that each of the MB subtypes play important but functionally distinct roles during encoding, consolidation and retrieval. One of the most striking findings in the literature, for example, is that expression of the *rutabaga* adenyl cyclase only in γ neurons can fully restore short-term memory (STM) to *rutabaga* mutants, whereas expression of NF1 in α/β neurons is sufficient to restore STM to NF1 mutants. Because these mutants each disrupt only a portion of STM performance, this has been taken as evidence that distinct signaling mechanisms support parallel memory traces within these two sets of neurons.

To test this model, we focused on the D1-like Dopamine receptor (DopR), mutations of which completely eliminate performance. We demonstrate that DopR expression in γ neurons is sufficient to fully support memory performance. Because of the known role of MB-MP1 DA neurons in mediating the US, we used GFP-reconstituted across the synapse (GRASP) to visualize synaptic connections between MB-MP1 and γ neurons. Our findings support a model in which the CS-US association forms solely in γ neurons. Subsequent memory processing then engages signaling in α/β neurons.

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Poster #51
Intermittent ethanol access increases ethanol intake in diverse mouse genotypes

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Rats and mice rarely achieve intoxicating blood ethanol levels or show signs of ethanol dependence under conditions of continuous, 24-hour free-choice access to ethanol, thus limiting the applicability of such studies to human alcohol abuse. Perhaps the simplest way to increase voluntary ethanol intake is to impose temporal limitations on ethanol availability. For example, schedules of intermittent 24-hour ethanol access reliably lead to escalation of ethanol intake in both rats and mice. Since previous studies of intermittent 24-hour ethanol access in mice have all been conducted in C57BL/6 mice, the present study explored the effects of intermittent access in a range of mouse genotypes characterized by diverse ethanol-related phenotypes. We assessed the effects of intermittent ethanol access in high-drinking C57BL/6J and low to moderate-drinking C3H/HeJ inbred mice, in selectively-bred “High-Drinking-in-the-Dark” (HDID1) and HS/Npt control mice, and in selectively-bred Withdrawal-Seizure-Prone (WSP2) and Withdrawal-Seizure-Resistant (WSR2) mice. While all tested genotypes displayed robust escalation of ethanol intake under both one-day-per-week and three-days-per-week access schedules, the magnitude of the intermittency effect varied across genotypes. Thus, C3H/HeJ mice showed the most dramatic effect, characterized by an approximate 4-fold increase in ethanol drinking, while the WSP and WSR lines showed the least dramatic effect, characterized by an approximate 30% increase in drinking. Surprisingly, there were no differences in escalation between HDID and HS/Npt mice or between WSP and WSR mice, indicating that alleles contributing to escalated drinking under intermittent ethanol access are largely independent of those underlying both binge-like drinking and withdrawal severity.

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Poster #52
A Drosophila Model for Transgenerational Epigenetic Inheritance

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Transgenerational epigenetic inheritance involves the inheritance of a phenotype across at least one generation that does not involve any changes in the DNA sequence. The primary mark of transgenerational epigenetic inheritance is thought to be DNA methylation, such as in imprinting in mammals and in the inheritance of coat color in Agouti viable-yellow (A^{vy}) mice. However, while most studies of Drosophila melanogaster indicate that there is no DNA cytosine methylation, nevertheless several systems of transgenerational epigenetic inheritance have been demonstrated in this organism. In this chapter, we review several Drosophila transgenerational epigenetic systems, including a system that we developed in our laboratory that involves the transgenerational epigenetic inheritance of an ectopic large bristle outgrowth (ELBO) in the eyes of Drosophila melanogaster that can be passed from generation to generation for hundreds of generations. Understanding transgenerational epigenetic inheritance mechanisms in Drosophila can have a profound impact in understanding similar processes in humans in which environmental exposures can affect the health of future generations.

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Poster #53
Effects of social separation on depression, anxiety, learning and memory in the 5XFAD mouse

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In humans, loneliness increases the risk of depression and of late-life dementia (Wilson et al, 2007, Arch. Gen. Psychiatry 64, 234-40). Social isolation also increases depressive-like behavior in female C57BL/6J mice (Martin & Brown, 2010, Behav. Brain Res. 207, 196-207). The aim of this study was to investigate the effects of social separation on behavior of male and female 5XFAD mice and their B6SJL wildtype (WT) littermates. Mice were housed in same-sex littermate groups until five months of age and then half were separated for one month before testing. Separated females, but not males, had reduced weight gain and increased wildness scores. Separation increased the frequency of bouts of immobility in the tail suspension test for both males and females. Separation did not affect measures of activity in the elevated plus maze or light-dark box but female 5xFAD mice showed less anxiety than WT females. There were no effects of separation on learning or memory in the Morris water maze, but separated mice showed less freezing in the contextual memory test. These results indicate that social separation results in an increase in depressive-like behavior in female mice but does not affect measures of activity, anxiety, spatial or conditioned fear memory. Although females seem more sensitive to the effects of social separation than males, the 5XFAD mice do not seem more sensitive than their WT littermates.

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**Poster #54**

**Associations between cannabinoid receptor-1 (CNR1) variation and hippocampus and amygdala volumes in heavy cannabis users**

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**Background:** Heavy cannabis users display smaller amygdala and hippocampus volumes, and genetic variation accounts for a large proportion of variance in liability to cannabis dependence (CD). A single nucleotide polymorphism in the cannabis receptor-1 gene (CNR1), rs2023239, has been associated with CD diagnosis and intermediate phenotypes, including greater abstinence-induced withdrawal, cue-elicited craving, and parahippocampal activation to cannabis cues. **Methods:** This study compared amygdala and hippocampus volumes between heavy cannabis users and healthy controls, and analyzed interactions between group, rs2023239 variation and the volumes of these structures. Ninety-four heavy cannabis users participated, of whom 37 (14 men, 23 women; mean age = 27.8 (SD = 8.7)) were selected to match 37 healthy controls (14 men, 23 women; mean age = 27.3 (SD = 7.9)) for case-control analyses. **Results:** Controlling for total intracranial volume and other confounding variables, cannabis users had smaller left amygdala (p < .05) and bilateral hippocampus (left, p < .005; right, p < .01) volumes than controls. When genotype was considered, there was a group by genotype interaction, such that the rs2023239 G allele predicted lower volume of bilateral hippocampus among cannabis users, but greater volume among controls (both p < .05). There were no group by genotype interactions on amygdala volume. **Conclusions:** These data replicate previous findings of reduced hippocampus and amygdala volume among heavy cannabis users, and suggest that CNR1 rs2023239 variation may predispose greater cannabis-related volume loss in the hippocampus. This association should be tested in future studies of brain volume differences in CD.

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Poster #55
The role of BK potassium channels in habituation and prepulse inhibition of startle

M Mirkowski, M Typlt, E Azzopardi, P Ruth, S Schmid

The acoustic startle response (ASR) is a protective behavioural response that is modulated by sensory gating processes, i.e. habituation and prepulse inhibition (PPI). Short-term habituation of startle has been studied in many animal models, but the underlying molecular mechanism has never been resolved. Studies in Aplysia and rodents have indicated an intrinsic, presynaptic and calcium dependent mechanism at the sensorimotor synapses of the reflex pathway as underlying mechanism. Furthermore, mutations in C. elegans and Drosophila have indicated that functional BK potassium channels are required for short-term habituation.

We here tested mice with and without a genetic disruption of the large conductance calcium activated potassium channel (BK channel) for short-term and long-term habituation of startle as well as for PPI. Although knock-out (KO) mice show obvious motor impairments, the average startle amplitude of KO-mice did not differ from those of wild-type (WT) animals. WT-animals habituated to 70% of their initial startle response, while no significant short-term habituation was observed in KO-animals. Habituation levels in heterozygous littermates were intermediate. None of the mice seemed to show long-term habituation. PPI was significantly attenuated in KO-mice when compared to WT-littermates and PPI in heterozygous mice was intermediate.

The data suggests that the activation of BK potassium channels in the brainstem is crucial for short-term habituation of startle, confirming invertebrate findings. Additionally, BK channels seem to play an important role in PPI, indicating that fine tuning of synaptic efficacy by BK channels may be more generally involved in sensory gating processes.

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Obesity is a major health problem in the USA. ADAR2 transgenic mice misexpressing either wild or mutant ADAR2 suffer from excessive overeating. ADAR2 is double stranded RNA binding protein that catalyzes the conversion of Adenosine to inosine (A to I). Since, inosine and guanosine have the same base pair properties, both transcriptional and the translational machinery reads inosine as guanosine (G). Hence this epigenetic phenomenon alters the biological properties of the serotonin C receptor (5HT2CR) and reduces the efficacy and potency of the receptor to serotonin signaling. To determine global mRNA changes in the hypothalamus, we have employed next generation sequencing combined with m-SEQ analysis on the isolated RNA from the hypothalamus. Sequencing was performed on total RNA from control and ADAR2-Tg mice. RNA from four individual mice per genotype was sequenced. Using DESeq, which uses a negative binomial model we found 592 genes with >2 fold log2 changes with an adjusted p-value <= 001 and out of which several genes are associated with feeding. The 5HT2CR is implicated in feeding and also a substrate for ADAR2. Therefore RNA editing and expression of the 5HT2CR were examined from the hypothalamus. We find significantly altered 5HT2CR RNA editing without any change in the 5HT2CR mRNA expression and coincide with significantly increased food intake in ADAR2 transgenic mice. Furthermore, selective 5HT2CR agonist significantly reduces food intake in obese leptin resistant ADAR2 transgenic mice. These results altogether suggest that 5HT2C may provide a common neurocircuitry to eating disorder of ADAR2 transgenic mice.

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Poster #57
Haplotype analysis of $PDE4D$ 83 (rs966221), $PDE4D$ 87 (rs 2910829), $PDE4D$ 32 (rs 456009) polymorphisms with stroke susceptibility in North Indian Population

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Stroke is an acute neurologic event leading to death or severe long-term disability. In the past decade, the widely studied candidate gene in stroke is $PDE4D$ (Phospho diesterase 4D) which was identified as the first novel gene associated with ischemic stroke. The role of genetic variants of $PDE4D$ in ischemic as well as hemorrhagic stroke susceptibility has not been explored in North Indian population. Therefore, we aimed to investigate the role of association of $PDE4D$ 83 T>C (rs966221), $PDE4D$ 87 C>T (rs 2910829), $PDE4D$ 32 G>A (rs 456009) polymorphisms with stroke susceptibility. 386 CT (computerized tomography) or MRI (Magnetic Resonance Imaging) proven stroke patients and 188 healthy volunteers were included in the study; 193 each had ischemic stroke (IS) and hemorrhagic stroke (HS). Ischemic stroke was classified into large vessel, small vessel disease stroke and hemorrhagic stroke in to nonlobar and lobar group. Genotyping was done by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism analysis. The genotype and allele frequency of $PDE4D$ gene polymorphisms were compared between patients and controls using SPSS ver 15. Haplotype analysis was done using Arlequin ver. 2.0

The 3 polymorphisms studied in $PDE4D$ gene ($PDE4D$ 83 T>C, $PDE4D$ 87 C>T, $PDE4D$ 32 G>A) were not associated with hemorrhagic stroke in total and in its subgroup. However, $PDE4D$ 83- CC genotype was significantly higher in ischemic patients (26.4%) as compared to healthy controls(20.2%) and was significantly associated with disease risk (OR=1.85 95%CI=1.03-3.31) $P$ value=0.03. Eight haplotypes were constructed for above 3 polymorphisms present at $PDE4D$ locus. The Yates’s corrected $P$ value and D’ between locus in controls is as follows; $PDE4D83^*PDE4D87$(P=0.02andD’=0.130), $PDE4D83^*PDE4D32$(P=0.21,D’=0.080),$PDE4D87^*PDE4D32$(P=0.65andD’=0.038). The frequencies of all 8 haplotype combinations were statistically similar in ischemic stroke patients as compared to controls. On the contrary, the frequency of haplotype $T_{83} T_{87} A_{32}$ was lower in hemorrhagic stroke compared to controls and showed protective effect for hemorrhagic stroke. However, on applying Bonferroni correction for multiple testing, we failed to find association of this haplotype with hemorrhagic patients.

Our study results suggests that only $PDE4D$ 83 T>C polymorphism is associated with ischemic stroke susceptibility in our patient population. The reason for no association of genetic markers or the haplotype studied in hemorrhagic stroke is not surprising as majority of our hemorrhagic patients had hypertension which is believed to be the most important risk factor for hemorrhages.

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Poster #58
Deficiency of Schnurri-2, an MHC enhancer binding protein, induces mild chronic inflammation in the brain and confers molecular, neuronal, and behavioral phenotypes related to schizophrenia

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Schnurri-2 (Shn-2), an NF-kB site-binding protein, tightly binds to the enhancers of major histocompatibility complex (MHC) class I genes and inflammatory cytokines, which have been shown to harbor common variant single nucleotide polymorphisms associated with schizophrenia. Although genes related to immunity are implicated in schizophrenia, there has been no study showing that their mutation or knock-out results in schizophrenia. Here, we show that Shn-2 knockout mice have behavioral abnormalities that strongly resemble those of schizophrenics. The mutant brain demonstrated numerous schizophrenia-related phenotypes, including transcriptome/proteome changes remarkably similar to those of postmortem schizophrenia patients, decreased parvalbumin and GAD67 levels, increased theta power on electroencephalograms, and a thinner cortex. Dentate gyrus granule cells failed to mature in Shn-2 knockout mice, a previously proposed endophenotype of schizophrenia. Shn-2 mice also exhibited mild chronic inflammation of the brain. These results suggest that genetically-induced changes in immune system may be a predisposing factor in schizophrenia.

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Poster #59
Behavioral effects of nicotine in α5 knock-out mice

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Nicotinic acetylcholine receptor (nAChR) subunit α5 is an accessory subunit that does not participate in the formation of the acetylcholine binding site but may have profound effects on e.g. ion permeability and desensitization properties of the nAChR channel. The α5 subunit is also involved in regulation of nicotine-induced behaviors. α5 knockout mice are resilient to the convulsant effects of acute nicotine.

In this study we explored whether α5 knockout mice show altered response to chronic nicotine. We administered nicotine as pulsed intravenous infusion and registered home cage activity and body temperature radiotelemetrically. In addition, we performed a standard acute behavioral test battery to compare the chronic and acute effects of nicotine. Furthermore, we used conditioned taste aversion and oral nicotine preference tests to probe the motivational effects of nicotine in α5 knockout animals.

Acute, α5 knockout mice were less sensitive to the hypoactivity- and hypothermia-inducing effects of nicotine. Male homozygous α5 knockout animals developed full tolerance to nicotine within approximately 6-8 hours from the onset of nicotine infusion, whereas the body temperature of wild-type males remained low during the entire 7-day nicotine treatment. Withdrawal did not have an effect on body temperature. Conditioned taste aversion test did not reveal significant genotype differences. α5 knockouts consumed more nicotine at higher concentration levels than did wild-type animals.

In conclusion, deletion of α5 subunit diminishes the acute behavioral sensitivity to nicotine and increases oral nicotine consumption. However, it does not affect nicotine-induced taste aversion or body temperature during withdrawal.

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Poster #60
The effect of dietary deficiencies during gestation on adult behaviors in mice.

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Exposure to dietary deficiencies during gestation has been shown to result in an increased risk for affective disorders in human populations. In utero exposure to nutrient deficient diets has been modeled successfully in rats, but very few studies have examined genetically stable mouse lines, for which many more genomic analysis tools exist. In a pilot study, we tested the effect of gestational and postpartum low protein, low Vitamin D and methyl deficiency on reciprocal F1 female offspring of C57BL/6J and NOD/ShiLtJ mice. Females were exposed to various diets for 5 weeks prior to mating and throughout pregnancy until weaning. Reciprocal F1 offspring were tested in a variety of behavioral assays to study the effects of gestational diet on anxiety and depression-related behaviors, sensorimotor gating, social interaction and locomotor response to psychostimulants. We observed significant reciprocal strain differences in novelty-induced locomotor activation and other behavioral measures. Diet-dependent, reciprocal cross differences were also observed for anxiety-related behaviors. Surprisingly, however, many behaviors in the F1 mice were largely unaffected by what would be considered severe dietary deficiencies in utero.

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Assessment of mouse line 129S6/SvEvTac as a model for post-traumatic stress disorder and other anxiety-like behaviors.

S.J. Temme¹, J. Slater², G.G. Murphy¹,²,³

Fear can be both adaptive and maladaptive. Maladaptive fear, such as fear that is persistent or easily generalized to nonthreatening stimuli, is often diagnosed as anxiety-related disorders in humans. Through Pavlovian fear conditioning, researchers have been able to study the formation of fear, as well as the reduction of fear through fear extinction. From these studies, research has found a strain of 129 steel mice known as 129S1/SvImJ, or 129S1, that display significant impairments in fear extinction and increased fear to a similar non-training setting compared to classically studied C57BL/6J mice. This suggests persistent and potentially overgeneralized fears that may represent an anxiety related disorder like phenotype. Using Pavlovian fear conditioning and extinction, as well as a protocol specifically designed to assess generalized fear, we evaluated a sub-strain of the 129 steel line known as 129S6/SvEvTac, for anxiety-related behaviors. Differences in the 129 sub-strains could lead to easily identifiable candidate genes for the study of persistent and generalized fear, as well as additional models for studying anxiety disorders. Our results show that, like 129S1 animals, 129S6 mice show normal levels of fear conditioning compared to C57BL/6J mice with significant impairments in extinction to conditioned cue or context, but normal levels of contextual fear generalization. This suggests that, like 129S1 animals, 129S6 mice exhibit anxiety related behaviors which could make them a good model for studying persistent, but not generalized fears. Direct comparisons of the 129S1 and 129S6 lines are in progress to fully understand these differences in fear expression.

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A widely held view is that the stress-responsive adrenergic system is critical to the consolidation of memory for emotional experiences. However, genetic evidence to support this view is lacking. For example, mice in which the adrenergic ligands norepinephrine and epinephrine (NE/E) are absent due to targeted disruption of the dopamine β-hydroxylase gene (Dbh) exhibit deficits in hippocampus-dependent aversive memory retrieval but intact consolidation of fear memory. Using pharmacologic and genetic approaches, we find that dopamine through D5 receptors signals in a redundant manner to NE/E through β2-adrenergic receptors to promote fear memory consolidation in the amygdala. This is mediated via mutual activation of phospholipase C rather than adenylyl cyclase. Further, stimulation of β2 receptors actually decreases levels of cAMP in the hippocampus, an effect that underlies the impairment of memory retrieval by stress and glucocorticoids. The consolidation and the retrieval effects of β2 receptors are mediated by their coupling to G\textsubscript{i/o} rather than to G\textsubscript{s}, while the effects of D5 receptors are mediated by their coupling to G\textsubscript{q}. The results demonstrate the need to revise the pervasive notion that adrenergic signaling is uniquely required for aversive memory consolidation through activation of β receptors and cAMP.
Poster #63
Interaction between promoter variants of the DRD4 gene and impulsivity in skiers and snowboarders.

C.J. Thomson\textsuperscript{1}, A.K. Rajala\textsuperscript{2}, N. Hase \textsuperscript{3}, S.R. Carlson\textsuperscript{4}, and J.L. Rupert\textsuperscript{1}.

Impulsivity and sensation seeking are personality traits that have often been associated with disinhibited behaviours including substance use and gambling, but have also been associated with sport practices. Twin studies have shown that impulsivity and sensation seeking are moderately heritable traits, and candidate genes involved in dopamine transmission have been targets for association studies. We analyzed five common polymorphisms in the promoter of the dopamine-4-receptor gene (\textit{DRD4} -1106T>C, -906T>C, -809A>G, -291C>T, 120-bp duplication) in a cohort of skiers and snowboarders, practitioners of high-risk (but commonly practiced) sports in whom we expected to see a large range of impulsive sensation seeking scores. We compared sensation seeking, impulsivity, and skiing behaviours (all previously shown to be correlated) between genotype groups in a sample of 450 skiers/boarders of at least intermediate ability. A multivariate analysis revealed an interaction between the 120-bp duplication and the -906 C>T (rs3758653) (Wilks’ Lambda = .98, \( p = .04 \)). Follow-up univariate analyses revealed the interaction was only significant for impulsivity scores (\( F(1,440) = 8.01, \ p = .005 \)). Individuals homozygous for both the 120-bp duplication and the -906C allele had higher impulsivity scores than those with the 120-bp duplication and a -906T allele. These results are consistent with two earlier family-based studies that reported preferential transmission of the -906C allele and behavioural impulsivity, and the 120-bp duplication and externalizing-related phenotypes.

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Poster #64
The IntelliCage as high-throughput behavioral screening tool: spontaneous behavioral profiles of strains, brain lesions and mutants

E Vannoni (1), V Voikar (2), G Colacicco (3), HP Lipp (1), DP Wolfer (1,4,5)

Traditional behavioral tests for mice are inefficient. They involve isolation, exposure to unfamiliar apparatus, and repeated handling. Resulting stress responses introduce artifacts and make testing unreliable. Automated assessment of behavior in the homecage may eliminate many of these problems. The IntelliCage collects individual data from socially housed RFID tagged mice and thus also eliminates isolation stress and enables parallel testing of large numbers of mice. While many specialized protocols have been developed for IntelliCage to test learning and memory, attention, impulsivity and emotional responses, all mice begin testing with some days of free adaptation. Spontaneous corner visits, nosepoking patterns and licking activity are already monitored 24/24h during this phase. We have collected data on 50 behavioral parameters of >800 mice. Subsequent factor analysis extracted 12 orthogonal factors accounting for 81% of total variance. Comparison of factor scores of C57BL/6, DBA/2, BALB/c and 129S2 mice revealed a unique profile for each strain. Analysis of mice with hippocampal, prefrontal and striatal lesions also yielded unique profiles for each condition. Monitoring of mutant mice with known deficits in hippocampus-dependent tests produced profiles very similar to those of hippocampal lesions. Thus, already the monitoring of spontaneous behavior during a few days of free adaptation to IntelliCage permits high throughput prescreening of mutant mice. On the other hand, our data indicate that tight control of genetic background remains essential also if behavioral testing occurs in the home cage.

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Poster #65
Genome wide gene expression analysis of saliva by psychosocial stressor exposure status: associations with tissue, clinical and organelle characteristics.

Aaron Wacholder1, Denise Nishita1, Jessica Bowers2, Judy A Andrews3, Andrew W Bergen1

We investigated genome-wide gene expression in whole saliva to identify biomarkers of exposure to psychological stressors and smoking. Saliva was collected from 48 individuals from the population-based longitudinal Oregon Youth Substance Use Project, stratified by psychosocial stressor exposure level measured by the Life Events and Difficulties Schedule. Genome-wide expression analysis was performed using the Affymetrix Gene ST 1.0 array. Independent component analysis suggested cellular heterogeneity in the saliva samples, with the first component corresponding to a division between cells with an expression profile similar to blood and cells with an epithelial-like expression profile. In a linear model, the third independent component was highly associated with psychosocial stressor exposure (p<.01) and smoking status (p<.001). Most mitochondrial genes on the Gene ST array are strongly associated with the third component, suggesting a potential link between psychosocial stressor exposure, smoking and mitochondrial activity. Additionally, differential expression analysis indicated several differentially expressed genes between high and low stressor exposure categories and between smokers and non-smokers with a 20% FDR after correcting for the first three independent components.

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Poster #66
Behavioral analysis and neurogenesis in mice overexpressing erythropoietin

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Erythropoietin (Epo) is produced in the kidneys under hypoxic conditions to increase erythrocytes. Healthy volunteers, psychiatric patients and healthy mice have been treated with acute injections of Epo showing positive effects on learning, memory, attention and mood. Both, Epo and its carbamylated derivate also increased neurogenesis in healthy mice. The aim of the present study was to investigate the effect of Epo on learning, memory and neurogenesis using two animal models that overexpress endogenous Epo: Tg21 mice chronically overexpressing human Epo in the brain only without any changes in blood parameters, and Tg6 mice constitutively overexpressing human Epo in both plasma and brain. Learning and memory were assessed by means of a wide range of conventional tests and the IntelliCage. To asses adult neurogenesis we quantified proliferating cells, young neurons (or young cells of the neuron lineage) and differentiating cells and total number of granule cells in the dentate gyrus. No differences were found between transgenic (either Tg21 or Tg6) and wild type animals in learning and memory in any of the tests. We found the expected differences between younger and older animals in proliferation and neuronal differentiation, but there was no difference between transgenic and wild type animals. The total number of granule cells was also similar in Tg21, Tg6 and wild type animals. In conclusion, we could not find any positive effect of chronic endogenous overexpression of Epo in learning, memory and neurogenesis, narrowing Epo's brain impact to the previous observation in reduced impulsivity and increased anxiety.

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Poster #67
A role for the \textit{Csnk1e} locus in opioid reward

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Studies in mice and humans indicate that the gene casein kinase 1-epsilon (\textit{Csnk1e}) contributes to the behavioral response to psychostimulants and opioids. We previously identified a quantitative trait locus on chromosome 15 near \textit{Csnk1e} (79.2 Mb) that influenced methamphetamine- and opioid-induced locomotor activity (congenic region = 78-86.8 Mb). B6.D2\textsuperscript{Csnk1e} congenic mice showed an increased sensitivity relative to B6.B6\textsuperscript{Csnk1e} congenic mice. Interestingly, this precise locus also affects ethanol consumption, further implicating a dopaminergic genetic mechanism. In the present study, we examined the effect of the \textit{Csnk1e} locus on the rewarding properties of the mu-opioid receptor agonist fentanyl using the conditioned place preference (CPP) assay. Twenty-four hours post-assessment of initial preference for the drug-paired side on Day 1, mice received fentanyl (0.05-0.2 mg/kg, i.p.) on Days 2 and 4 on one side of the open field and saline (i.p.) on Days 3 and 5 on the other side (distinguished by visual and tactile cues). Seventy-two hours later (Day 8), mice were assessed for fentanyl-CPP (Day 8 – Day 1). Similar to the locomotor findings, B6.D2\textsuperscript{Csnk1e} mice showed an enhanced fentanyl-CPP at lower doses (0.05-0.1 mg/kg). However, at the highest dose (0.2 mg/kg), B6.D2\textsuperscript{Csnk1e} mice showed a marked reduction in fentanyl-CPP which was now much lower than B6.B6\textsuperscript{Csnk1e} mice. This may indicate that B6.D2\textsuperscript{Csnk1e} mice are also more sensitive to the aversive properties of opioids which are recruited at higher doses. In summary, the \textit{Csnk1e} locus significantly modulates the motivational properties of opioids. Future experiments will employ direct gene and pharmacological targeting of \textit{Csnk1e}.

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